Department for Science, Innovation & Technology

Department of Health & Social Care

Office for Life Sciences

Independent report

Commercial clinical trials in the UK: the Lord O'Shaughnessy review - final report

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Contents

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Foreword

The UK is blessed with a rich, diverse and creative academic sector with 4 of the world's 10 leading universities in the field of international research (https://www.topuniversities.com/university-rankings/world-university-rankings/2023). Matched with an entrepreneurial culture that is second only to the United States, this makes our science sector the envy of the world. But in the fields of medicine and life sciences, inventions and discoveries alone do not change lives. For a therapy, device, diagnostic or digital tool to reach patients, a long, often laborious process of translating insights into products and then testing their safety and efficacy through clinical trials is required.

The UK has a magnificent track record in this area, both in our historic achievements and recent successes, such as the COVID-19 vaccine and therapeutic trials. These pandemic experiences showed the UK's clinical research base at its best – a dynamic partnership of government, academia, industry, the NHS and the public, all aligned on the urgent need to develop treatments to prevent or treat an urgent health need. The RECOVERY trial and COVID-19 Vaccine Taskforce (VTF) showed what we are capable of when we put our minds to it.

Case study: the Vaccine Taskforce

Set up by and as part of UK government in April 2020, the UK Vaccine Taskforce took a dynamic and innovative approach to accelerating vaccine development, leading to one of the most successful vaccine roll outs globally. This resulted in millions of people in the UK and around the world being able to receive a COVID-19 vaccine. Bringing together government, academia and industry, the VTF was created to develop and produce a vaccine for COVID-19 as fast as possible. The VTF had 3 main objectives. To:

- secure access to promising COVID-19 vaccines for the UK population as quickly as possible
- make provision for international distribution of vaccines
- strengthen the UK's onshoring capacity and capability in vaccine development, manufacturing and supply chain to provide resilience for future pandemics (https://www.gov.uk/government/publications/the-vaccine-taskforce-objectives-and-membership-of-steering-group/vtf-objectives-and-membership-of-the-steering-group)

Led by Kate Bingham, and as a joint unit between the Department for Business, Energy and Industrial Strategy (BEIS) and the Department of Health and Social Care (DHSC), the VTF contributed early funding for clinical trials of the Oxford-AstraZeneca vaccine, supporting developers to run their own clinical trials, as well as commissioning and managing independent investigator-led trials. The Vaccine Taskforce also provided £38.8 million in

funding to vaccine research, including the ComCov and CovBoost studies, which were world-first studies on interchanging different types of COVID-19 vaccines. The findings from these studies have helped inform the UK's COVID-19 vaccination programme as well as vaccine policy around the world.

Together with UK Research and Innovation (UKRI), the National Institute for Health and Care Research (NIHR) commissioned research through a rapid call in February to March 2020, including funding for the development of the Oxford-AstraZeneca vaccine. The VTF contributed funding for the subsequent clinical trials of the vaccine. NIHR provided critical infrastructure, funding and expertise, including research teams to undertake key policy research critical for effective implementation, and the timing and use of booster doses.

Three key elements then helped to ramp up pace and scale of vaccine delivery. Firstly, the vaccine trial was one of a limited number of studies that was prioritised for delivery by a UK-wide expert panel based on criteria set by England's Chief Medical Officer.

Secondly, a regional model to support the rapid delivery of vaccine studies was created, with vaccine research delivery hubs set up across the UK to support multiple large-scale vaccine trials. This was established within weeks under the leadership of the NIHR Clinical Research Network (CRN) with NIHR local clinical research networks (LCRNs) in England and the devolved governments drawing together a multitude of partner organisations.

Finally, recruiting vaccine trial volunteers at pace was a priority. The NHS COVID-19 Vaccine Research Registry, developed by NIHR, the VTF and NHS Digital, was launched in July 2020, allowing people to sign up to participate in trials. Vital in recruiting a diverse set of participants to over 14 vaccine trials, the first 100,000 volunteers for vaccine trials were registered by mid-August, with the registry reaching its target of 500,000 volunteers in June 2021.

Post-pandemic, we continue to perform strongly in recruiting patients to academically driven clinical trials. The number of patients taking in part in these kinds of studies have reached over 1 million in 2021 to 2022, and the vast majority – around 98% – of patients recruited to clinical studies in the NIHR Clinical Research Network portfolio are recruited to trials with a non-commercial sponsor (https://www.nihr.ac.uk/about-us/who-we-are/our-research-performance/annual-statistics.htm).

Unfortunately, in recent years the UK has been falling behind in its commercial clinical trials activity. Numbers of patients enrolled onto commercially-led studies supported by the NIHR dropped by 44% between 2017 to 2018 and 2021 to 2022, according to Association of the British Pharmaceutical Industry (ABPI) research – from around 50,000 a year to around 28,000 (https://www.abpi.org.uk/publications/rescuing-the-uk-industry-clinical-trials/).

Similarly, we are falling behind in the number of trials initiated, particularly for phase 3 trials, with our relative ranking against other countries dropping from 4th to 10th best in the world in the same timeframe. Countries like Spain and Australia

have stolen a march on us, with companies choosing to initiate more trials in each of these countries compared to the UK, in what is an increasingly competitive global marketplace (https://www.abpi.org.uk/facts-figures-and-industry-data/clinical-trials/global-data/global-rankings-number-of-industry-clinical-trials-initiated-in-2021-by-country-by-phase). Other countries, such as Poland, have been able to recruit high numbers of patients for each commercial trial, with an average of 61 participants in phase 2 and 3 trials compared to an average of 21 per trial in the UK between 2018 and 2020 (https://www.abpi.org.uk/facts-figures-and-industry-data/clinical-trials/global-data/average-number-of-participants-treated-per-industry-clinical-trial-by-country-by-phase-2018-2020/).

There are many reasons why this is important. First and foremost, it reduces the opportunities of British patients to have early access to innovative treatments that could improve, extend or even save their lives. Hospital consultants who take part in research studies are more likely to promote the uptake of innovative therapies or devices once they have been licensed, improving access for all patients. NHS bodies that carry out research tend, on average, to provide better health outcomes for their patients (https://www.rcplondon.ac.uk/projects/outputs/benefiting-research-effect). Encouraging more research must be a priority for those bodies charged with improving the nation's health.

Second, falling levels of commercial research create a significant opportunity cost for the NHS itself. Therapies and healthcare services that would otherwise have been funded by a pharmaceutical or technology company instead have to be funded by the taxpayer, and the financial benefit that commercial research generates for NHS providers – which comes from companies, not taxpayers, and which can be used to provide better services locally – is lost. Research carried out for this report suggests that the total direct cost of the near halving of patients recruited to commercial research activity in the NHS over the last 5 years is in the region of £360 million, funding that has to be found from the taxpayer instead. Over this time period, an additional estimated £570 million could have been provided to the NHS to recover costs of running commercial trials. This is based on OLS analysis of the impact and value of the NIHR Clinical Research Network report (https://www.nihr.ac.uk/news/new-report-highlights-how-nihr-support-for-clinical-research-benefits-the-uk-economy-and-nhs/22489).

Third, it reduces the desirability of the UK as a destination for life science investment and impedes the uptake of health innovations. According to polling carried out by H/Advisors Cicero, 86% of industry executives believe that increasing industry clinical trial activity in the UK is important or very important for the next government (https://cicero-group.com/2023/04/03/life-sciences-industry-insights/). The government has rightly declared that it wants the UK to be a science superpower, with the life sciences an area of strategic focus. Delivering on that ambition requires a range of actions on regulation, data access and pharmaceutical pricing, for example – and increasing the attractiveness of the UK as a site of commercial research is one area that industry has identified as a priority.

Commercial research associated with the NIHR Clinical Research Network generated £1.8 billion in gross value added (GVA) to the UK economy in 2018 to 2019 (https://www.nihr.ac.uk/news/new-report-highlights-how-nihr-support-for-clinical-research-benefits-the-uk-economy-and-nhs/22489). The UK has a vibrant and growing life science industry which generated £94.2 billion in turnover in 2021, a value that has seen continuous growth in real terms since 2013. Sites involved in research and development (R&D) generated nearly a third, £29.2 billion of this turnover (https://www.gov.uk/government/statistics/bioscience-and-health-technology-sector-statistics-2021). Attracting more of this inward investment to the UK will create more high-quality jobs, bring more medicines to market and provide more tax revenues for the state.

So even though commercial trials are a relatively small part of the UK's overall clinical research activity, they have a disproportionately large role in delivering better health and wealth for our citizens. There are areas of outstanding practice in the UK, where what we do is genuinely world-leading. One of the review's objectives was to learn from excellence – at home and abroad – and outline how, through comprehensive reform, these examples of exceptional practice can become the norm. Throughout the review report are case studies outlining UK successes (with the NHS-Galleri trial first, below) to demonstrate what is possible.

We can do so much better than we currently are, and everything I have heard from clinicians, patients, researchers, NHS bodies, industry and others during the course of this review reveals a strong desire to regain our world-leading position in this area. I am confident it is possible, which is why I have proposed that the government should aim to double the numbers of people taking part in commercial clinical trials in the next 2 years, and double it again by 2027.

Case study: the NHS-Galleri and GRAIL trial

The NHS Long Term Plan sets out an ambition to diagnose three quarters of all cancers early by 2028. The NHS-Galleri trial is being run across our nation by the Cancer Research UK & King's College London Cancer Prevention Trials Unit (CPTU), in partnership with NHS England and healthcare company GRAIL Bio UK Ltd, that developed the Galleri® test. The study is helping us to better understand how a new blood test for cancer would work in practice. Using a sample of a person's blood, Galleri can detect a common cancer signal across many different types of cancer and direct the diagnostic path with a high degree of accuracy.

The aim of this trial is to see if using the Galleri test alongside existing cancer screening in the NHS can help reduce late-stage diagnoses, making cancer potentially easier to treat. The trial has recruited over 140,000 volunteers in just over 10 months, making it one of the fastest recruiting cancer diagnostic studies. To date, study retention remains high, reflecting participants' engagement with the trial.

This study required invitations for volunteers whose age (between 50 and 77 years), locality, gender, ethnicity and socio-economic status were known and aligned with risk factors for developing cancer, but not yet diagnosed and treated for cancer in the last 3 years. The NHS-Galleri trial team worked closely with NHS DigiTrials to offer a streamlined approach for data-led recruitment. Following approvals, invites were sent using data from routinely collected national NHS datasets to identify the right and representative participants.

The NHS-Galleri trial demonstrates the benefit for large-scale, fast recruiting trials of using innovative trial approaches to facilitate more diverse and representative trial recruitment than has been achieved through traditional methods.

At a time of such remarkable therapeutic innovation, there is increasing interest across the world in the development of new financially sustainable trial delivery models with the ability to deliver clinical trials to regulatory standards in collaboration with clinical academic networks. Models such as LYSARC (the Lymphoma Academic Research Organisation) (https://lymphoma-research-experts.org/lysarc) in France, HOVON (the Haemato Oncology Foundation for Adults in the Netherlands) (https://hovon.nl/en/about-hovon) in the Netherlands and the CIBMTR (Center for International Blood and Marrow Transplant Research) (https://www.cibmtr.org/Studies/ClinicalTrials/Pages/index.aspx) in the USA are reportedly proving highly effective at attracting inward investment by the global pharmaceutical sector. The NHS is ideally placed to build on this principle, which would create a vibrant sector complementary to the current contract research organisation (CRO) model to the benefit of patients, the NHS and the UK life sciences economy.

Regaining our global leadership position is not simply a case of reinvigorating our clinical trial activity along traditional lines - although we need that, too. It also means using our regulatory, funding and policy levers to create an environment where innovative forms of trial can flourish. We should be leveraging our strategic advantages in genomics, cell and gene therapies, and precision medicine to provide more trials for advanced therapies. And there is also an opportunity to gain a global leadership position in the field of digital or decentralised approaches that enable people to take part in research through their GP or even at home.

Pushing research closer to people will increase public interest and involvement in research and will help to make sure that it is as inclusive as possible. Life science companies want and need to make sure their trial cohorts are as diverse as possible so that they can prove, with confidence, that their medicines will benefit people from all ethnicities and backgrounds. This works to our benefit, too, because the groups who gain most from taking part in more diverse research cohorts are precisely those people whose health needs are greatest and who are therefore of most interest to researchers. This points to the tantalising possibility of research being used systematically by health boards and integrated care systems to reduce health inequalities, a goal we all share.

This independent review was commissioned by HM government to put forward ideas on how we can both reverse our decline and transform the commercial clinical trials environment. Supported by the Office for Life Sciences, I have engaged with dozens of representatives – and received many submissions and data – from industry, the NHS, universities, clinicians, patient groups, regulators and others to bottom out the problems and develop solutions. In doing so, despite the explicit focus of the review on commercial trials, I am acutely aware that this must not be a zero-sum game and that any proposals that benefit commercially led research should not be to the detriment of academic studies and provide an overall improvement in clinical trials activity. Our success in early-stage and academic-led research is a strength to be celebrated and anything that changes because of this review should not reduce UK competitiveness here.

This review was commissioned by UK government ministers to make recommendations on how to improve the environment for running clinical trials in the UK. Although ministers in the devolved governments were not involved in the original commission I received, I have been keen to ensure that the review delivers recommendations that improve competitiveness across the whole of the UK. To this end, officials for devolved administrations have attended workshops and joined discussions at various UK meetings. While a greater focus has been given to the systems and structures in England, many of the recommendations made in this review are applicable to the whole system, across all 4 nations of the UK, and I hope they will be seriously considered by their governments.

The recommendations seek to improve all the critical capabilities needed to undertake a successful commercial clinical trial in the UK, from workforce and patient engagement through to set-up times, approvals processes, data access and how we incentivise each part of the system to undertake more research. They build on a range of actions already underway (or committed to) which will help improve our performance in commercial trial activity. We have surveyed all the relevant government bodies and their commitments in this area are reflected within the ‘foundational actions’ part of this review. We have recommended adding SMART objectives to make sure they have real bite and that their implementation can be reviewed objectively.

Beyond these existing foundational actions, which will help bend the performance curve a little, the report proposes a range of ‘significant actions’ that should bend that curve more dramatically. Some of these will pay dividends in the short-run, others will take longer to come to fruition, but all are intended to deliver major, sustained growth in commercial trial activity. Critically, these actions should promote traditional ways of doing trials as well as innovative methods. The partnership between 2 very different UK life science success stories – AstraZeneca and Huma – shows the potential of the UK in this field.

Case study: AstraZeneca and Huma partnership

Digital health technologies can provide significant benefits for the clinical trials of new treatments. By enabling decentralisation, data can be collected from the

comfort of participants' homes, reducing or eliminating the need to travel to clinical trial sites; a more diverse patient group can be reached; and better patient recruitment, retention and adherence to the trial protocol through an improved experience can lower the overall cost of research.

In March 2022, AstraZeneca, a global, science-led biopharmaceutical company headquartered in the UK, took a step towards harnessing this technology-driven, decentralised clinical trial opportunity through its partnership with Huma Therapeutics, a leading global digital health company also headquartered in the UK.

Huma's technology platform is founded on the first and only disease-agnostic software as a medical device (SaMD) to hold EU Medical Device Regulations (MDR) class IIb certification status. Its adaptations are used on a global scale by more than 1.8 million patients across around 3,000 hospitals and clinics and by more than 650,000 participants across research. Through Huma's primary care division, iPLATO Healthcare, whose digital service is used by 31 million people across the UK, digital technology is also driving recruitment into the UK's largest research programme, Our Future Health, through text messages and push notifications to invite people to join this incredible research programme.

Partnering with Huma enables AstraZeneca to conduct clinical trials in an entirely new way. For example, a global decentralised study of AstraZeneca's COVID-19 vaccine was designed to allow participants to report data on mobile phones across multiple continents, without ever visiting a trial site. In Germany, Huma and AstraZeneca worked together on a real-world evidence study to identify patients at risk of developing chronic kidney disease, resulting in the potential to recruit 7,000 patients in a single month.

These are powerful examples of a global pharma leader partnering with a British technology company to show the potential of digital-first care and research.

By combining digital technology with investigational research, AstraZeneca and Huma believe that this innovative approach will deliver marked improvements in the clinical trials space, ultimately resulting in the faster delivery of new and better medicines to patients in the UK and worldwide.

Finally, I recommend that all the governments of the UK – either individually but ideally collectively – should hold a competition to create an initial set of clinical trial acceleration networks (CTANs) that would be designed, funded and equipped to deliver genuinely best-in-world clinical trials services in areas of critical strategic interest for the UK's health and life sciences sectors.

Different implementation options should be considered for the CTAN programme. They could focus on the 8 life science missions, like neurodegenerative disease and respiratory disease, or areas of science where the UK has global leadership, like cancer vaccines or cell and gene therapies. An alternative approach would involve being open to other areas of scientific discovery that offer transformative

potential, along the lines of the approach that Advanced Research and Invention Agency (ARIA) has taken to recruiting its first wave of programme directors. Whichever way they are created, the aim of the CTAN programme is to provide an opportunity for the excellence that too often occurs in spite of the system to be used as an engine of change that transforms and becomes the system.

There are many proposals outlined in the review, but perhaps one thing more than any other needs to change: the attitude of everyone involved in health and care – public, patients, clinicians, NHS managers and politicians – towards the role of clinical trials in society. If the UK is truly going to be a science superpower, we have to use every asset at our disposal. There is no reason why this cannot happen: we have the workforce, the scale, the data, the science base, the research charities and many other strengths, but arguably none is more significant than the NHS.

A public commitment from leaders across the UK demonstrating that it is our ambition for the NHS to become the world's leading platform for health and life sciences research, followed by a comprehensive plan of reform and a targeted set of key performance indicators (KPIs) against which progress can be transparently judged, would be a powerful signal of intent. And this signal must enable research to be prioritised within the context of the intense pressure that health and care services are under, and the demand for capacity, recognising the potential for research to transform care for the future.

Executive summary

This review was commissioned to offer recommendations on how commercial clinical trials can help the life sciences sector unlock UK health, growth and investment opportunities. The sector was also asked to advise on how to resolve key challenges in conducting commercial clinical trials in the UK. Extensive engagement with leaders from industry, medical research charities, academia, the NHS, regulators and other partners in clinical trials has highlighted a high degree of consensus about both the areas of UK success, and where action is needed to further competitiveness. The 27 recommendations of the review are set out below.

Delivery partners across the system in the NHS - regulators, funders and policy makers - have previously committed to a range of actions to tackle the challenges that the UK faces in clinical trials, including in attracting commercial trials. This review aims to build on that pre-existing work. Therefore, the first recommendation is as follows:

Recommendation 1

Develop and publish SMART (specific, measurable, achievable, relevant and time-bound) metrics for all the ambitions in the clinical research vision Saving and Improving Lives: The Future of UK Clinical Research Delivery (https://www.gov.uk/government/publications/the-future-of-uk-clinical-research-delivery/saving-and-improving-lives-the-future-of-uk-clinical-research-delivery), and

subsequent implementation plans, with owners held to account for delivery by the Life Sciences Council.

Other recommendations

The remaining recommendations aim to build on this existing programme of work and transform the UK environment for commercial clinical trials. The recommendations are set out according to a series of statements of the problems they are intended to solve.

Problem statement 1: clinical trial set-up and approval processes in the UK are slow and bureaucratic, especially compared to other countries

Recommended significant actions

Recommendation 2

The Medicines and Healthcare products Regulatory Agency (MHRA), Health Research Authority (HRA) and other system leaders should set up a rapid ‘task and finish’ group to produce a plan on reducing the regulatory burden of approving trials and removing delays in set-up, including with the goal of reaching a 60-day turnaround time for all approvals.

Recommendation 3

On receipt of this plan, additional funding should be provided by the UK government to the regulators, the MHRA and the HRA, to rebuild capacity and deliver reduced turnaround time for all approvals.

Recommendation 4

A comprehensive and mandatory national approach to costing and contracting should be developed and instigated, in partnership with industry.

Problem statement 2: lack of transparency and data about commercial clinical trials activity in the UK

Recommended significant actions

Recommendation 5

The MHRA, the HRA, the NIHR and its equivalent organisations across the UK should collect, consolidate and publish national monthly returns on all the clinical

trials activity that is happening in the NHS, and NHS bodies and commercial sponsors should publish numbers of patients in trials on a monthly basis.

Recommendation 6

Building on near real-time activity and performance generated according to the above recommendation, UK governments should create a UK phase 1 to 4 clinical trial directory – called ‘clinicaltrials.gov.uk’ – to create a single source of activity for patients, clinicians, researchers and potential trial sponsors.

Problem statement 3: lack of accountability at every level for underperformance in clinical trials

Recommended significant actions

Recommendation 7

DHSC, the Department for Science, Innovation and Technology (DSIT) and the NHS should set stretching annual targets for increasing commercial trials in the 4 countries of the UK and carry out annual benchmarking exercises comparing performance against competitor countries. Central to this ambition should be the objective of doubling recruitment to commercial clinical trials within the next 2 years, with a further doubling by 2027.

Recommendation 8

A new UK-wide set of KPIs for clinical trials should be established covering all critical aspects of the approval and set-up of and recruitment to trials, an overall measure for UK performance in clinical trials, and outcome measures for the impact of commercial trials. These KPIs should apply to all bodies involved and be benchmarked against global exemplars.

Recommendation 9

In England, a new operating model for the NIHR CRN should be introduced to strengthen accountability and delivery.

Problem statement 4: research is not systematically prioritised by or within the NHS

Recommended significant actions

Recommendation 10

A statement should be made by the NHS leadership and ministers of the UK’s intention for the health service to be the world’s leading platform for health R&D,

and annual R&D targets should be introduced for the NHS at every level.

Recommendation 11

The business development service in NIHR and its equivalent bodies should be set explicit performance targets to increase the number, kind and diversity of commercial trials.

Problem statement 5: doctors, nurses and NHS organisations lack incentives to take part in research, especially when it is commercially-funded

Recommended significant actions

Recommendation 12

Income generated by commercial sponsors should be explicitly directed to units and departments leading trials in NHS sites to provide direct financial incentives to take part in commercial trials.

Recommendation 13

The NHS should use the upcoming NHS Long Term Workforce Plan and UK Recovery, Resilience and Growth (RRG) Research Workforce Strategy to establish a Clinical Trials Career Path for training critical roles for research.

Problem statement 6: conversations about research are absent from many interactions between clinicians and patients. The topic has a low profile with the public, especially among disadvantaged or marginalised groups

Recommended significant actions

Recommendation 14

An ongoing public campaign should be conducted to promote research and to generate evidence on the most effective communication methods, in partnership with medical and research charities.

Recommendation 15

Full integration of NIHR Be Part of Research (https://bepartofresearch.nihr.ac.uk/) with the NHS App should be accelerated, with enhanced opportunities to take part in clinical trials added to the platform.

Recommendation 16

The government and the NHS should work with royal colleges and unions to integrate ‘research conversations’ into all NHS communications and clinical interactions.

Recommendation 17

Specific targets should be introduced for the new Research Delivery Network (RDN) co-ordinating centre and regional centres to expand research to multiple sites, and to increase diversity of patients recruited.

Problem statement 7: we are failing to take advantage of the NHS’s considerable data assets

Recommended significant actions

Recommendation 18

Agencies responsible for information governance within clinical trials should establish a common approach to contacting patients to take part in research within the current legislative framework.

Recommendation 19

All patients receiving genomic sequencing of any kind in the UK should be offered a standard consent for engaging in research.

Recommendation 20

A national participatory process should take place on patient consent to examine how to achieve greater data usage for research in a way that commands public trust. This should seek to establish a publicly supported position around the proactive contacting of patients to take part in trials that could form part of their care.

Recommendation 21

The NHS England Data for R&D Programme’s NHS Research Secure Data Environment Network should be rolled out, including urgent publication of guidance for NHS bodies on engaging in research with industry.

Problem statement 8: primary care is a negligible provider of clinical trial activity, despite the opportunities it provides for delivering population-scale trials, and there is too much reliance on hospital settings for the delivery of trials.

Recommended significant actions

Recommendation 22

Financial incentives should be introduced for GPs to take part in commercial trials.

Recommendation 23

New primary care research networks should be introduced to increase the proportion of commercial trials taking place in primary care and ‘at home’ settings.

Recommendation 24

Regulators should produce guidance to support and promote innovative and decentralised trials.

Recommendation 25

The government and regulators should develop a strategy for the use of AI in clinical trial design and regulation.

Clinical trial acceleration networks (CTANs)

For each of the steps of the process of establishing and running a clinical trial in the UK, the above actions recommended by the review will aim to improve the system for all trials, but to truly transform performance, a more innovative approach is required.

Recommendation 26

A new ‘enhanced service’ option should be developed, through the proposed clinical trial acceleration networks (CTANs) to enable government and the NHS to develop an excellent process for every step of a trial for specific areas, both to further research in the selected fields and to prove the case and create an exemplar for improving the service for all trials in the future.

Implementation

To ensure effective oversight of the implementation of these recommendations, an action plan should be published, and reported on publicly every year.

Recommendation 27

An action plan should be developed, to report by autumn 2023, outlining how the government and delivery partners will implement the recommendations of this review. The Life Sciences Council should provide objective accountability for the delivery of this action plan by the government and its agencies.

Part 1: context, operating environment and existing commitments

Introduction

During the engagement that has taken place over the last few months, I have been impressed by the high degree of latent entrepreneurialism among frontline staff and the strong desire among many clinicians to take part in research across the NHS. This is despite the extraordinary pressures that most health workers are under and the ongoing need to recover from the pandemic. I have also heard of many areas and instances of excellence across the country. Case studies of some of these are provided throughout the report, demonstrating what the NHS and wider UK ecosystem is capable of with the right leadership, culture and resources.

Unfortunately, despite the positive intentions of many staff, these examples of excellence in commercial trials are too often atypical. There is a large degree of variation in performance in different phases of trials; while the UK was ranked fourth in the number of commercial phase 1 trials initiated in 2021, behind the USA, China and Australia, the UK's ranking fell to tenth for commercial phase 3 trials (https://www.abpi.org.uk/facts-figures-and-industry-data/clinical-trials/global-data/global-rankings-number-of-industry-clinical-trials-initiated-in-2021-by-country-by-phase/). We have heard from industry that the UK is viewed as an unreliable and unpredictable partner. Our approvals processes are theoretically competitive but inconsistent because of backlogs at the MHRA and unnecessary site-level approvals processes, which create delays. One major global pharmaceutical company that submitted evidence to the review said that, of the 18 European countries in which it carried out research, the UK was the second slowest for setting up clinical trials. This is clearly unacceptable for a country with our resources and ambitions.

The comparative data backs this up: when measuring the time from application for regulatory approval to delivering the first dose to a participant for a selection of trials in 2020, the median time for the UK was 247 days, with the USA, Spain and Australia all achieving median times of under 200 days. The USA was quickest at 155 days (https://www.gov.uk/government/publications/life-science-sector-data-2022). Industry reports that because of the UK's under-performance we generally get much lower allocations from global pharma for recruitment numbers compared to other countries. From a submission to the review, one of the largest global pharmaceutical companies reported a 60% decrease in patients they recruited to trials in the UK between 2019 and 2021, with a further significant drop expected in 2022. We often underperform against reduced targets, getting lower allocations in the following year, and so on down the spiral.

Nor are those other countries just sitting still; many are surging ahead and, having taken much of our previous trial activity, want to take the rest. In 2021, there were 394 commercial trials initiated in the UK (interventional trials that have begun to recruit patients), compared to 471 in Spain, and all European countries were substantially behind China and the USA, with over 1,110 and nearly 2,000 initiated (https://www.abpi.org.uk/facts-figures-and-industry-data/clinical-trials/global-data/number-of-

industry-clinical-trials-initiated-per-year-by-country-2012-2021/). Furthermore, the global clinical trials sector is developing rapidly, with new approaches and innovative trial design pushing trials closer to patients, and currently other countries look more attractive for these trials than we do. Denmark, for example, launched guidance on the implementation of decentralised elements of clinical trials in 2021 and is encouraging these trials through collaboration between the regulator and clinicians, companies and patients (https://laegemiddelstyrelsen.dk/en/news/2021/guidance-on-the-implementation-of-decentralised-elements-in-clinical-trials-with-medicinal-products-is-now-available/).

Annex A, 'Defining terms and scope', sets out a summary of the UK clinical trials system and defines the scope of this review. The terms of reference for the review, and the list of stakeholders who engaged with it have also been published alongside this report.

The importance of global competitiveness in clinical trials

Although the UK performs well in many aspects of clinical trial research, such as initiation of phase 1 trials, a highly competitive global market for clinical research makes it crucial the UK remains ambitious on the world stage to capitalise on its strengths. As wider opportunities for new technologies and treatments become widely available to patients worldwide, the UK needs to remain in step with globally competitive set up and approval times if it is to be an attractive place to invest and to avoid patient care being compromised.

Realising health benefits

A globally competitive clinical trials ecosystem in the UK is vital in enabling us to tackle the UK's most pressing healthcare priorities, contribute on the world stage and attract investment. Over 1.2 million people took part in clinical research in 2021 to 2022 in the UK (https://www.nihr.ac.uk/about-us/who-we-are/our-research-performance/annual-statistics.htm) and there are opportunities to expand this further given the UK's excellent research ecosystem, its world leading science and research base, our globally respected regulators, and our strengths in cutting-edge innovation – from novel cancer vaccines to precision medicine.

Research has been shown to improve survival rates for patients and the care they receive, along with having a positive impact on the NHS and its staff. For the NHS, trusts that are more research-active benefit from the 'research effect', as described by the Royal College of Physicians (https://www.rcplondon.ac.uk/projects/outputs/benefiting-research-effect). Its report demonstrates how instrumental clinical research is in driving patient care. For example, a study on patients with colorectal cancer found that mortality was 30% lower in the first 30 days after major surgery in trusts with high levels of research participation compared to trusts without. Research participation improves job satisfaction for clinicians, helping them build new transferable skills, preventing burnout and supporting the retention of staff. This drives better care for patients and improved Care Quality Commission (CQC) ratings.

Driving economic growth and generating revenue for the NHS

As well as significantly improving patient outcomes, clinical research has clear benefits in supporting UK economic growth. NIHR CRN supported commercial and non-commercial research provided over 47,000 full time equivalent jobs and generated £2.7 billion gross value added (GVA) in 2018 to 2019. Around two-thirds (£1.8 billion) of the £2.7 billion in GVA generated was from commercial clinical trials activity funded by the life sciences industry (https://www.nihr.ac.uk/news/new-report-highlights-how-nihr-support-for-clinical-research-benefits-the-uk-economy-and-nhs/22489).

Return on investment from clinical research is made up of direct health benefits to patients, profits to UK firms undertaking research funded or supported by NIHR, and spill-over returns to the wider economy, including indirect health benefits (https://www.gov.uk/government/publications/the-future-of-uk-clinical-research-delivery). Commercial sponsors of trials also pay to run trials, which generates direct income for the NHS, as well as cost savings because the costs of treating patients in the trials are met.

Clinical trials are a vital part of a vibrant UK life sciences sector, which has continued to grow over recent years, with £94.2 billion in turnover in 2021, a 9% increase from 2020 with an upward trend since 2013 (https://www.gov.uk/government/statistics/bioscience-and-health-technology-sector-statistics-2021). The business sector in the UK performed £5 billion of pharmaceutical R&D in 2020, and this has consistently accounted for around one fifth of R&D performed by companies across all sectors of the economy between 2014 and 2020 (https://www.gov.uk/government/publications/life-science-sector-data-2022). Although 32% of life science sites in the UK participated in R&D in 2021, this proportion has stagnated in recent years (https://www.gov.uk/government/statistics/bioscience-and-health-technology-sector-statistics-2021).

In 2018 to 2019, the NHS received an estimated income £355 million from life science companies and saved an estimated total of £28.6 million from pharmaceutical cost-saving, where a trial drug replaced the standard of care treatment. From 2016 to 2017 to 2018 to 2019, for each participant recruited onto a clinical trial, on average, the NHS received over £9,000 in income from life science companies and saved nearly £6,000 due to treatment costs being covered by the commercial sponsor. This is the pharmaceutical cost saving for each patient recruited, where a trial drug replaced standard of care treatment (https://www.nihr.ac.uk/news/new-report-highlights-how-nihr-support-for-clinical-research-benefits-the-uk-economy-and-nhs/22489).

If the UK was able to bring about positive change to its clinical research ecosystem there could be significant economic benefits. A return to 2017 to 2018 levels of recruitment could result in an additional income of £200 million and savings of £127 million in one year, in 2018 to 2019 prices. If the patients enrolled in commercial trials had remained at the same level as in 2017 to 2018, the NHS would have generated an estimated £570 million in income, and £360 million in

savings in the intervening years (https://www.nihr.ac.uk/news/new-report-highlights-how-nihr-support-for-clinical-research-benefits-the-uk-economy-and-nhs/22489).

Importantly, analysis has shown that the cost savings to the NHS are substantial from companies conducting their trials in the UK, even before the cost savings and benefits of the discovery of more cost-effective treatments resulting from clinical trials are taken into consideration.

UK performance in clinical trials

While a substantial number of people across the UK participate in clinical research sponsored by either a hospital or academic institution, only a small minority of people are currently participating in commercial trials sponsored and funded by pharmaceutical, biotech and medtech companies. The number of participants in commercial research, supported by NIHR, has substantially declined from over 50,000 patients in 2017 to 2018 to just over 28,000 in 2021 to 2022, the lowest number of patients recruited in the last 7 years (https://www.abpi.org.uk/publications/rescuing-the-uk-industry-clinical-trials/). Greater Manchester has bucked the trend and increased the number of patients recruited to commercial trials activity in recent years with a 44% increase in patients from 2017 to 2018 to 2021 to 2022 (https://healthinnovationmanchester.com/partnerships/manchester-academic-health-science-centre/).

Although the number of commercial studies in the NIHR portfolio reached its highest number in 7 years in 2021 to 2022 (https://www.nihr.ac.uk/about-us/who-we-are/our-research-performance/annual-statistics.htm), the UK has not seen as many trials initiated as other similar countries in recent years. In 2021, there were 394 trials initiated in the UK compared to 471 in Spain, but all European countries were substantially behind China and the USA, with over 1,110 and nearly 2,000 initiated respectively (https://www.abpi.org.uk/facts-figures-and-industry-data/clinical-trials/global-data/number-of-industry-clinical-trials-initiated-per-year-by-country-2012-2021/).

Case study: Greater Manchester

The NIHR Greater Manchester CRN (NIHR GM CRN) and its regional health and social care providers have become a hub of commercial research delivery. Thanks to NIHR GM CRN's strong research infrastructure and talented workforce, collaboration between providers, academia and industry, and a supportive business environment, NIHR GM CRN has a successful record of supporting life sciences research across a range of therapeutic areas and trial phases.

NIHR GM CRN beat national average times of study set up, accelerating their regional site start up timelines to an average of 51 days, in comparison to the national median for commercial study set up of over 117 days since 2019. Similarly, while an average of 60% of trials deliver to time and target across

England, NIHR GM CRN has consistently recruited above the target of 80% for the last 10 years. While there has been a 36% decrease in national commercial study recruitment over the last 6 years, NIHR GM CRN has achieved a 19% increase.

NIHR GM CRN works closely with industry partners and in industry clusters to deliver high-quality research studies that meet the needs of both local communities and international sponsors. The NIHR GM CRN network has invested for over 10 years in a single leading business unit of research delivery experts who assist and expedite the initiation and delivery of commercial research, as an NIHR CRN GM dedicated team of staff employed solely to work on NIHR CRN Commercial studies headed up by an Industry Operations Manager. This team works with a deliverability process, which is centred on site engagement, specialty leadership, rapid resolution pathways and collaboration with regional site management organisations.

NIHR GM CRN has initiated a consent for contact registry, developed feasibility and recruitment systems, embedded digital connectivity, and has recently procured a mobile research unit. These services evolve through continual stakeholder feedback and proactive key account management, as part of the NIHR GM CRN progressive Business Development programme, which includes local health and care providers regularly coming together with companies to discuss key issues and future ambitions.

There is a large degree of variation in performance in different phases of trials globally: while the UK was ranked fourth in the number of phase 1 trials initiated in 2021, behind the USA, China and Australia, the UK's ranking fell to tenth for phase 3 trials (https://www.abpi.org.uk/facts-figures-and-industry-data/clinical-trials/global-data/). Through the review, we have heard from numerous leading sponsors of commercial clinical trials, who report a drop off in investment in UK clinical trials. From a submission to the review, one of the largest global pharmaceutical companies reported a 60% decrease in patients they recruited to trials in the UK between 2019 and 2021, with a further significant drop expected in 2022.

Impact of COVID-19 on clinical research

The UK was successful in recruiting over a million participants into COVID-19 research over 2020 to 2021, leading to UK-led research delivering the world's first effective COVID-19 treatments, approving a vaccine and identify dexamethasone as a treatment. However, this pivoting to COVID-19 research meant that set up and recruitment times for non-COVID-19 commercial research was affected by the impact of the pandemic and the continued pressure on services across the NHS.

Approval, set-up and recruitment times for non-COVID-19 trials in 2020 were severely impacted by the COVID-19 pandemic when the UK, like many countries, diverted research efforts to COVID-19 (although other European countries recruited lower numbers of people into COVID-19 research). Evidence

demonstrates that clinical research in other countries, particularly in Europe, recovered more quickly from the pandemic.

A managed approach to the recovery of the UK clinical research portfolio in the NHS is being implemented, aiming to achieve a recovery of clinical research in the NHS. This is called the Research Reset Programme, which launched in March 2022; prior to this there was a programme called Managed Recovery. This approach was developed through the UK Clinical Research Recovery, Resilience and Growth (UK RRG) Programme, led by DHSC, and managed by DHSC and NHS England (NHSE).

DHSC and NHSE set out a case for change that underpinned a decision to implement the Research Reset programme in early 2022, which included the acknowledgement that UK clinical research competitiveness had been significantly affected, with reductions in the number of international studies planned for the UK and reductions in headcounts seen across UK affiliates of multinational companies, making the UK less attractive as a destination for new research.

The Research Reset programme aims for 80% of all open studies on the NIHR CRN portfolio to be delivering to time and target by June 2023. As of April 2023, 65% of all (including commercial and non-commercial) studies were delivering to time and target (https://sites.google.com/nihr.ac.uk/thefutureofukclinicalresearch/home/research-reset/progress-update).

Time for set-up and approval of trials

Once a trial has been planned, the sponsor must obtain approvals from regulatory bodies - principally the MHRA and the research ethics committees (RECs), depending on the type of trial. There is no requirement for site-level approval, but evidence gathered by this review and others demonstrates that requirements imposed by trusts create delays to progressing trials. Trial sites, whilst not required to carry out approvals, do need to complete capacity and capability checks to ensure that they have the resources in place to run a trial.

When comparing the timelines for clinical trials to be approved and set up in the UK to other similar countries, the UK performs poorly compared to others. Spain is often highlighted as an international leader in clinical trials. It has achieved a vast improvement in set up and approval times by introducing legislation (a Royal Decree) to mandate strict timelines for approval. This is cited as having reduced the time to set up a trial by 15% in the first year (https://pharmaboardroom.com/country-reports/spain-pharma-report-september-2019/). The time taken to set up and approve commercial clinical trials is substantially faster in both Australia and Spain compared to the UK. The median time in Australia and Spain in 2020 was 182 and 197 days respectively compared to 247 in the UK (https://www.gov.uk/government/publications/life-science-sector-data-2022).

In comparison, UK set-up times have been getting longer since 2018, when the median time was 222 days. There has been an increase in time taken for set-up

and approval for most other comparator countries over the same period, with some countries such as France and Canada seeing steep increases in 2020 compared to 2019. As a result, the UK has moved from having the longest time in 2019 to ranking seventh in 2020 out of 10 similar countries (https://www.gov.uk/government/publications/life-science-sector-data-2022). While this is a relative improvement, clearly longer absolute set-up times are not something to be celebrated.

In 2022, combined review from the MHRA and the NHS HRA was implemented for all clinical trials aiming to streamline the approval process and speed up the time to plan, set up and run a trial. Combined review was shown to reduce the time taken for trials to be approved in the UK, with the median time for approval for trials reviewed through combined review at 61 days in 2021 compared to 90 days for trials not included in combined review (https://www.gov.uk/government/publications/life-science-sector-data-2022). Despite the progress combined review made in lowering approval times up the end of 2021, the review has received evidence from commercial sponsors that there has been delays since the beginning of 2022 due to MHRA backlogs.

Updated data will be published as part of the 2023 edition of the Office for Life Science competitiveness indicators, which will include:

- the time for set-up and approving clinical trials (median time from clinical trial application to first dose to first patient) for 2021
- approval timings that cover the end-to-end timings for combined review from both the HRA and the MHRA for 2022

The HRA has already set a target to complete the ethical review within 60 days, with 97% of full reviews through combined review achieving this and a median time of 36 days between April 2022 and September 2022. The HRA has also set a target of getting this figure up 100% (https://www.hra.nhs.uk/about-us/who-we-are/meeting-minutes/board-agenda-papers-and-minutes/16-november-2022/).

Given the need for efficient and fast review of trials, the HRA's new fast track service offers a 50% faster ethics approval to provide a consistent and efficient approval process (https://www.hra.nhs.uk/about-us/news-updates/fast-track-review-clinical-trials-non-covid-19-research-continue/). This has been shown to substantially reduce the period for ethics approval, with a median time of 16 days in August 2022 and 27 days in September 2022 (https://www.hra.nhs.uk/about-us/who-we-are/meeting-minutes/board-agenda-papers-and-minutes/16-november-2022/). In March 2023, the MHRA also set new targets for application review within a maximum 30 days in general, with a maximum 10 calendar days for a decision to be granted once the regulator has received any final information (https://www.gov.uk/government/news/mhra-to-streamline-clinical-trial-approvals-in-biggest-overhaul-of-trial-regulation-in-20-years).

UK strengths in clinical trials

The UK has an excellent science base and world-leading institutions. Some of the qualitative input to the review has suggested that there has been a shift in the composition of the trial portfolios of many of the major UK centres in the last 5 to 10 years towards early phase trials and other experimental medicine studies. A strong science base is undoubtedly a major attraction of the UK for the pharmaceutical industry because it underpins the UK's capacity and capability for the entire national research portfolio, including commercial trials. It is critical to the future of UK life sciences that the country maintains a strong academic-led UK clinical science base.

Vibrant life sciences sector

The UK has a prestigious life sciences sector that is a central pillar of the UK's accomplishment as a prevailing centre for science and innovation, generating a turnover of £94.2 billion and employing 282,000 people in 2021 (https://www.gov.uk/government/statistics/bioscience-and-health-technology-sector-statistics-2021). The UK's success is driven by a strong ecosystem of academic excellence, world leading R&D, long-standing infrastructure investments, and the amazing data resources of the NHS. The dynamic nature of this sector is stimulated by collaborations between government, industry, universities and medical research charities. The strength of these partnerships and ability for the system to support industry are demonstrated by the UK being the first in the world to produce and approve a COVID-19 vaccine. Furthermore, by being global leaders in pioneering technologies, such as cell and gene therapies, the UK harnesses the power of transformative medicines and tackles the latest healthcare challenges.

Examples of world-leading performance in clinical trials

One demonstration of the collective power of the NHS, research institutions and the life sciences sector are the examples of the UK using these strengths to deliver innovative, large scale and globally unique trials for the benefit of patients.

Case study: BioNTech

Driving research and accelerating clinical trials for cancer immunotherapies is the foundation of the UK government's innovative partnership with world-leading biotechnology company BioNTech.

The collaboration aims to deliver a national advance on shared aspirations for personalised immunotherapies, including mRNA-based immunotherapies, chimeric antigen receptor T cell therapy (CAR-T), bi-specific antibodies and antibody drug conjugates (ADCs) to treat cancer by 2030, through UK trials involving up to 10,000 UK patients.

BioNTech has worked closely with DHSC and the NHS to solve the unique challenges in delivering BioNTech's innovative cancer therapies and vaccine trials in the UK. This has created awareness and momentum for brand new

infrastructure for a new referral network (the Cancer Vaccine Launch Pad) that will cast the screening net wider than ever before to ensure more eligible patients can take part in cancer vaccine clinical trials.

Taking lessons learnt from the pace of COVID-19 vaccine development and an agile and pragmatic approach, the accelerated trials aspiration that BioNTech and the NHS and NIHR are working on includes the following components to achieve excellence:

- bringing together key parts of the system early, for example, BioNTech has engaged with NHS and NIHR to discuss requirements and solutions to achieve rapid trial set up
- accelerating clinical trial contracting and exploring how to build improvements to the national contract value review (NCVR) to speed up trial opening
- BioNTech providing the NIHR with advance sight of BioNTech's pipeline of immunotherapy clinical trials, so they can work together proactively to engage the research community and prepare trial sites to sign up
- empowering clinical networks, NHS national leads, NIHR Experimental Cancer Medicine Centres (ECMCs) and academic leadership have worked with BioNTech to optimise trial delivery by collaborating on protocols, identifying national co-ordinating investigators and support with site selection and capacity planning. This will ensure uptake and timely enrolment of participants
- expanding patient access, using the pioneering NHS Cancer Vaccine Launch Pad (CVLP) to screen patients and streamline the sampling, and eventually sequencing (locally), of tumours for cancer vaccines

Case study: RECOVERY trial

As highlighted in the government policy paper 'Saving and Improving Lives: The Future of UK Clinical Research Delivery', the COVID-19 RECOVERY trial demonstrates the excellence that the UK can achieve in delivery of innovative and large-scale trials. The trial, led by the University of Oxford with funding from UKRI's Medical Research Council (MRC) and NIHR, and delivered with the support of the NIHR CRN, is the world's largest randomised controlled trial for COVID-19. Set-up in record-time in the early stages of the pandemic, with support from the NHS DigiTrials service, RECOVERY identified the first proven treatment for the virus and has provided other vital evidence about which treatments work and which do not.

This trial shows the enormous benefit of cross-sector partnership - the trial was funded by MRC and NIHR, sponsored by University of Oxford, conducted across every acute NHS trust, and studied generic, patented and novel treatments. For example, Roche provided 2,000 courses of the arthritis drug, tocilizumab, for use in the trial. On the basis of positive, life-saving results,

Roche has now obtained full licensing for its use for severe COVID-19 from 35 regulatory authorities, including the MHRA, European Medicines Agency (EMA) and US Food and Drug Administration (FDA).

Work ongoing to improve UK clinical trials

There is a wealth of existing evidence about the performance of UK clinical trials, and there have been a number of reports and reviews published both by government and by external organisations. Accordingly, delivery partners across the system in the NHS, regulators, funders and policy makers have already committed to actions to tackle the challenges that the UK faces in clinical trials, including in attracting commercial trials. This review aims to build on that pre-existing work and the high degree of consensus on some of the actions that need to be taken, and not to duplicate this work. The 'foundational actions' set out where these actions are already committed to, and the evidence that delivery partners have provided for confidence in delivery.

Driving this process is the UK RRG Programme, a UK-wide initiative that aims to:

- ensure the restoration of clinical research activity that was underway pre-COVID-19
- maximise opportunities to build back a better research ecosystem
- deliver on the commitment to make the UK the leading global hub for life sciences

The programme reports on progress on a dedicated site (https://sites.google.com/nihr.ac.uk/thefutureofukclinicalresearch/home/research-reset/progress-update) to provide updates on the commitments made in the Saving and Improving Lives: The Future of UK Clinical Research Delivery (https://www.gov.uk/government/publications/the-future-of-uk-clinical-research-delivery) and associated implementation plans. The UK RRG programme is led by DHSC, with members across devolved governments, regulators, NIHR, NHS organisations and industry and medical research charity representatives.

This collaborative approach has resulted in a strong programme of work, underpinned by a clear direction of travel in resolving issues in UK competitiveness. The work of this review has included examining these plans and working with system leaders on what work is already being completed and where there are blockers which, if removed, could help to boost the work of the UK RRG programme to allow the UK to go further and faster in delivery on its ambitions in clinical trials. Those discussions have highlighted a consistent theme in how improvements should be made to the existing work in train: to develop clear and measurable metrics of progress and highlight the work that is ongoing to improve confidence.

Highlights and examples of successes of existing work of the UK Clinical Research Recovery Resilience and Growth

programme

As outlined above, the DHSC and NHSE work to recover clinical research and reset the UK's research portfolio following the COVID-19 pandemic aims to restore a diverse and balanced study portfolio. Research Reset aims for 80% of all open studies on the NIHR CRN portfolio to be delivering to time and target by June 2023. The trend for this is improving, with the latest figures indicating that the percentage of open studies delivering to time and target was 65% in April 2023 up from a baseline of 27% in May 2022. 5,954 studies (including both commercial and non-commercial) are currently on the portfolio, down from a peak of 6,838 in February 2022 and are returning to similar levels seen before the pandemic. 80% of studies are open and recruiting, and the remaining 20% of studies are in set-up, which is near pre-pandemic levels. However, there are still a disproportionately high number of commercial studies in set-up, as commercial studies make up 30% of the whole portfolio, but account for over half of those in set-up (PDF, 335KB) (https://drive.google.com/file/d/1rmvgzcpM_4qHVXPaJo_Sp7mE9dHmYeKT/view).

As part of delivering on the 'Saving and Improving Lives: The Future of UK Clinical Research Delivery' vision through the UK RRG programme, delivery partners have signed up to a shared commitment to public involvement in research. This work is led by NIHR and the HRA. The aim is to maximise the reach, relevance and impact of research by ensuring a consistent and collaborative approach across the sector to involving patients and public in the shaping and conduct of research and recruiting participants into studies and trials. There was a meeting of the group responsible for delivery of this commitment in April 2023, to agree the planned programme of work. As part of delivering on the commitment, a number of delivery partners across the UK have taken actions, including:

- in Health and Care Research Wales, independent board members are being added to NHS organisations to promote research, and to increase the diversity of membership of the organisation's Involvement Community
- the Association of Medical Research Charities has developed new organisational commitments to help share best practice and learning between members, highlighting innovative approaches to involve patients and the public in a meaningful way; reviewing internal approach to encourage and support patient centricity, including working with others to ensure patient voice is appropriately represented; and, recognising the diversity of membership, supporting charities to include the patient voice at different stages of the research lifecycle, signposting resources and identifying areas that need further thought and discussion
- NHSE has published Increasing diversity in research participation: a good practice guide for engaging with underrepresented groups (https://www.england.nhs.uk/aac/publication/increasing-diversity-in-research-participation/), which provides practical insights for researchers on how to engage more diverse participants in health research
- NIHR Be Part of Research (https://bepartofresearch.nihr.ac.uk/) provides an online service that makes it easy for people to find and take part in health and care research. It shows what research is currently happening across the UK via the

website and through the NHS App in England. Across the UK clinical research system, organisations, including medical research charities, are working together to increase the racial, age, gender and geographic diversity of clinical trial participants, including the development of novel processes and guidance to increase uptake among traditionally underserved communities, underpinned by the HRA's work on people-centred research

- NIHR and NHSE have also begun work to collect and analyse the diversity of research participants. The first report was published in November (https://www.nihr.ac.uk/documents/randomised-controlled-trial-participants-diversity-data-report/31969) and shows that, of the 148 randomised control trials (RCTs) considered between April 2019 and March 2021, participants were: of a large range of ages; broadly equal across sex (49% male, 51% female); and mainly white – with 86% of participants being white.

In efforts to improve study set-up speed and efficiency, NHSE's NCVR, supported by NIHR, has led to some improvement in set-up times as a result of expedited and standard costing. In the first stage of implementation of the NCVR, which was operationalised in October 2022, all commercial contract research studies being submitted for a study resource review have entered the NCVR process. These are subject to a single costing negotiation organised by the lead site using a standard methodology. Information is available to companies prior to site selection on whether NHS sites will accept the interactive costing tool (iCT) generated cost without further negotiation. The next phase of the NCVR is in development.

The HRA has worked with colleagues in the devolved governments and a range of stakeholders to develop and expand the range of model UK contracts agreed with industry and the NHS. The model agreements for drug and device studies have been updated, including for use in primary care settings, and the first UK templates for non-interventional commercial research published. Unmodified use of the appropriate template site agreement is mandated by NHSE's national directive for commercial contract research and is a condition of the HRA and Health and Care Research Wales approval. In addition, the first UK template non-disclosure agreement to streamline information-sharing in site selection and set-up has been published.

In addition to the HRA's work to streamline approvals, it is continuing to offer a faster research ethics review for non-COVID-19 clinical trials in the UK, following a pilot in 2021. From August 2022, this service has been integrated into the wider REC structure to make it more sustainable in future, so that more RECs can accept fast-track reviews.

The ECMC network, with support from the MHRA and the HRA, has completed the initial intelligence-gathering phase of a project to radically accelerate the set-up of phase 1 oncology trials, which will be further developed with stakeholders including regulators, sponsors, R&D teams and investigators, to co-create new ways of working and pilot new approaches. An entry point to the ECMC has been provided through the ECMC Industry Engagement team, which has built relationships with partners across the clinical research ecosystem, including clinical research organisations, biotech and NIHR.

In addition, an increase of engagement with companies has resulted in an increase in commercial trial opportunities coming to the ECMC network. There has been engagement with approximately 80 pharmaceutical, biotech, clinical research organisations and academic institutions since 2016 and, out of the more than 320 opportunities that have come to the ECMC network, approximately 80% have been commercial.

The combined review from the MHRA and the UK Research Ethics Committee (REC), in collaboration with the HRA, facilitates speedier set-up for clinical research trials. Since January 2022, all new clinical trials of investigational medicinal products (CTIMPs) in the UK have been benefiting from the combined review, halving the approval time compared with separate applications over the period 2018 to 2021.

Work by the MHRA is underway to improve clinical trials regulation in a joint initiative between the MHRA, the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC) and All Wales Therapeutics and Toxicology Centre. This joint initiative, the Innovative Licensing and Access Pathway (ILAP), smooths the path through development for market for innovative treatments and has resulted in over 100 innovation passports issued.

Work is also underway by the MHRA, the HRA and the devolved governments, following consultation, to address clinical trials regulation by developing new UK legislation for clinical trials, which is planned to be laid before Parliament in 2023 (https://www.gov.uk/government/consultations/consultation-on-proposals-for-legislative-changes-for-clinical-trials/proposals-for-legislative-changes-for-clinical-trials).

In efforts to align clinical research capability towards the most pressing challenges facing the NHS, a new UK-wide accreditation scheme for clinical research practitioners (CRPs) aims to double the size of the workforce in the future, achieving a membership of the CRP directory of over 1,300 by April 2022, with resultant progression to individuals joining the Academy of Healthcare Sciences (ACHS) Accredited Register for CRPs.

In improving data access, up to £200 million of funding was committed to support NHS-led health research on 2 March 2022, to invest in health data infrastructure to support research and development in England, with parallel activity in the devolved governments.

Foundational actions

Although there is a defined process for delivery partners to provide updates on their commitments in the clinical research vision, these updates are lacking in specificity and clarity of ambition. Engagement with stakeholders through the review has highlighted many instances of a lack of awareness in the sector of the work that is ongoing, which demonstrates the need to better publicise the efforts being made to improve the system. Where there is awareness of the work, there is a low level of confidence in its successful delivery. All organisations across the UK RRG programme should be made responsible for developing SMART objectives

for their commitments and providing transparent reporting on progress against these objectives. The detailed reporting should be provided to the Life Sciences Council via the Life Sciences Vision Delivery Board, and summaries should be published on the existing UK RRG site.

The first recommendation is to:

Recommendation 1: Develop and publish SMART metrics for all the ambitions in the clinical research vision Saving and Improving Lives: The Future of UK Clinical Research Delivery, and subsequent implementation plans with owners held to account for delivery by the Life Sciences Council

Part 2: problem statements and significant actions

Introduction

As should be clear from part 1, rebuilding and innovating within the UK's clinical trials sector is an essential part of the UK's wider health, scientific and economic strategy. Our early-stage trial activity has grown in recent years, and even in the declining sphere of commercial trials there are initiatives that have bucked the overall trend and demonstrate the ways in which we can overcome systemic challenges that, post-COVID-19, are still holding us back.

However, this begs the question: if we are clearly capable of delivering world-leading performance, why are these initiatives the exception and not the norm in commercial trials? What is it about the way that commercial research is funded, incentivised and delivered that stops NHS bodies pursuing more research activity to generate financial and other benefits for their staff and patients?

Based on the extensive engagement that has taken place during this review, below are a set of 8 problem statements that have come through most clearly as inhibiting the latent entrepreneurialism within the NHS to carry out more commercial trials. They reflect the range of inputs, including testimonies, submissions, data and literature, among others, received or explored as part of the review. They provide the framework for the actions that I believe the UK government, devolved governments, NHS and others need to undertake to set us on a different path.

Under each of the problem statements, this report puts forward a set of recommended actions that seeks to address and overcome them. Individually, each should help improve our clinical trials performance, and collectively these recommended actions would deliver a step change in activity with the goal of doubling commercial clinical trials recruitment within 2 years, and then doubling it again by 2027.

Problem statement 1: clinical trial set-up and approval processes in the UK are slow and bureaucratic, especially compared to other countries

The UK environment, with a single-payer health system and excellent science base, should provide a globally attractive environment for conducting clinical trials. However, we have heard from industry leaders that the reality is very different. The UK system is seen as complex and difficult to navigate, slow and unreliable in fulfilling its commitments, and lacking proactive 'customer management' to help shepherd companies through the quagmire.

Trial planning and set-up

The review has heard that too many hospital trusts, where the vast majority of clinical research takes place, carry out their own bespoke processes for the set-up and costing of trials, which adds to the time and cost of set-up. Life sciences companies can be just as guilty, insisting on numerous renegotiations that further slow down clinical trial initiation. The advent of national costing has been a welcome step forward, but it does not seem to be enforced and does not cover all the critical steps in the process of setting up trials.

NHS trusts also report that less-complex protocols, which are less likely to require amendment later, and fewer amendments from trial sponsors throughout delivery would help to reduce pressure on trial sites, freeing up capacity for trial delivery. The HRA leads the UK-wide contracting group, which has published a suite of model contracts, and has further templates planned (https://www.myresearchproject.org.uk/help/hlptemplatesfor.aspx).

Although efforts, such as the NCVR, are intended to streamline costing and contracting, achieving this goal is undermined by inconsistent take up by NHS trusts. The latest data collection shows that 53% of providers accept the costings generated by the iCT as part of the NCVR. As ABPI outlined in its 2022 report, unpredictable set-up timeframes reduce the time global industry clinical trials have to recruit in the UK, contributing to the UK's poor performance in trial recruitment and reducing industry's confidence in placing trials in the UK (https://www.abpi.org.uk/publications/rescuing-the-uk-industry-clinical-trials/).

There are some successes in this field across the UK, as all NHS organisations in Wales and Scotland adhere to costings generated by the iCT, for example. ABPI, UKRD and the Shelford Group are exploring how we can accelerate use of model contracts and drive adherence to iCT-generated prices for costings, across sites and sponsors. International examples demonstrate the impact that a standardised process for costing can have. For example, France is cited by ABPI as one of the quickest countries for the set-up and approval of trials, and has a mandated contract template with no flexibility for negotiations and a comprehensive list of costed items (https://www.abpi.org.uk/r-d-manufacturing/clinical-research/an-opportunity-for-growth-clinical-research-in-the-uk/), for which negotiations are limited mainly to a single co-ordinating site.

One of the reasons cited for inconsistent take up of model agreements for contracting, or costing through the NCVR, is the risk, or perceived risk, of carrying out clinical trial activities to the trial sites themselves, which results in duplicative due diligence and other compliance checks. There are existing indemnity schemes covering some of the risks associated with clinical trial activity: the HRA has confirmed that (https://www.hra.nhs.uk/about-us/news-updates/indemnity-cover-nhs-staff-delivering-research/) 'the Clinical Negligence Scheme for Trusts (CNST) and Clinical Negligence Scheme for General Practice (CNSGP) provide cover against harm to patients arising from clinical negligence in the conduct of research' and 'the Liabilities to Third Parties Scheme (LTPS) provides cover for Employer Liabilities in the conduct of research'.

However, these do not cover all the risks of research perceived by NHS organisations, which includes the risk of action by the Information Commissioners Office (ICO), Care Quality Commission (CQC), Human Fertilisation and Embryology Authority (HFEA), the MHRA, or the Administration of Radioactive Substances Advisory Committee (ARSAC).

Contributors to the review have also highlighted that, for streamlined costing and contracting processes to be successful, there needs to be action taken by both NHS organisations and commercial sponsors of trials. Just as NHS bodies can be unwilling to accept contracting and costing decisions made by the lead site in a trial, we have received examples of companies modifying model agreements, such as adding additional terms into appendices, and failing to meet agreed timelines for supplying approved contracts or full documentation for trials.

Feedback from industry demonstrates that another issue in planning trials in the UK is the lack of a single view of research capacity and performance, meaning that commercial sponsors cannot obtain a central assessment of which NHS sites have the capacity to run trials or where relevant patient populations are based. Then, when sites are approached to conduct a trial, they often run capacity and capability checks in sequence, a time-consuming process that could be done in parallel to each other, and to other checks and approvals, such as with REC or the MHRA, to save time in this early stage of planning a trial.

Approvals

Cuts to regulators have been a major contributing factor to underperformance in set-up and approval times for the UK. While some regulators, such as the HRA, have been able to maintain service levels due to a continual programme of efficiency and improvement activity, the loss of strategic capacity and capability in other regulators, especially the MHRA, has been the single most common complaint from contributors to this review. The resulting delays to set-up and approval times are a significant impediment to siting more trials in the UK.

The review has also heard that there is a culture of nit-picking on the finer points of clinical trials delivery, with back and forth between sites and the regulator and sometimes companies themselves, which adds time and frustration to the process and is often repeated site after site. This compares with other countries where, if

templates have been followed and trials signed off by chief investigators (CIs), trials are usually given the go-ahead with limited or no revision. For example, in the USA, once 30 days have elapsed since submission of a study to the FDA, the sponsors can proceed with the trial whether they have received a response or not (https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application).

One of the UK clinical trials landscape's key strengths is the international reputation of its regulators, including the MHRA. However, industry leaders report that, although the the MHRA as an organisation takes a future-looking approach to innovation, it is under-resourced, resulting in a backlog of approvals, causing delays and providing a barrier to recruiting and retaining the most talented regulatory leaders at all levels. Contributors to the review have outlined that the capacity of bodies such as the MHRA and the HRA needs to be expanded to make the most of post-Brexit regulatory opportunities and address ongoing implementation challenges for innovative initiatives, such as the ILAP, as well as improving join-up across the system so that products that are expedited at some parts of the process also receive rapid approvals for clinical trials.

A large global pharmaceutical company has provided specific evidence about the impact of MHRA delays, with delayed enrolment to 13 trials between September 2022 and February 2023. This stakeholder also highlighted, as did many others, that it is not only the delays in MHRA processes, but the lack of communication and transparency about the delays themselves and how the MHRA is prioritising cases which prevents companies from effectively planning trials. This impacts both confidence in the UK as a clinical trial location and the ability of companies to plan ahead and make informed decisions about placing clinical trials in the UK, as evidenced by a submission to the review.

One of the measures taken to improve the speed of approvals is the MHRA and HRA combined review process. All trial applications that need approval from both regulators in the UK are now subject to combined review. However, delays due to backlogs in MHRA approvals risk negating any progress combined review has achieved. As a result, much more needs to be done to address MHRA resourcing issues to return to their previous performance levels (https://www.hra.nhs.uk/about-us/who-we-are/meeting-minutes/board-agenda-papers-and-minutes/16-november-2022/).

Recommended significant actions

Recommendation 2: the MHRA, the HRA and other system leaders should set up a rapid task and finish group on reducing the regulatory burden of approving trials, and removing delays in setup, including with the goal of reaching a 60-day turnaround time for all approvals

The MHRA and the HRA have set improved performance targets for both the MHRA and REC that will be embedded in the new clinical trial regulation. They include completing an initial review within 30 calendar days, with a maximum of 10 calendar days for a decision from receipt of responses to any request for further information (RFI) (https://www.gov.uk/government/news/mhra-to-streamline-clinical-trial-approvals-in-biggest-overhaul-of-trial-regulation-in-20-years). The UK RES already has a

target of completing reviews in 60 days and is achieving the successful implementation of its fast-track service ethics review.

However, these improvements must go further to achieve world-leading set-up and approval times. The regulators should set up a 3-month task and finish group to look at how it can further safely reduce the regulatory burden of setting up trials. This could be by removing unnecessary steps in the process, or by mandating parallel rather than sequential approvals processes for all regulatory aspects of clinical trial approval.

It is important for all parts of the UK to have equal opportunity to participate in clinical trials, and unless additional regulatory support is provided this may be a particular challenge for Northern Ireland as a consequence of regulatory divergence from the rest of the UK.

Therefore, the MHRA and the HRA should provide dedicated resource to address and overcome any regulatory barriers to Northern Ireland's participation in clinical trials and to enable the same KPIs to be delivered as in the rest of the UK, ensuring that any additional requirements for funders and partners in the NHS system are minimised.

Recognising the importance of the combination of approval processes and set-up processes, the task and finish group should consider the issues together - by looking to address both delays in regulatory approvals, and burdensome checks and duplicative processes at site level.

Recommendation 3: on receipt of this plan, additional funding should be provided by the UK government to the regulators, the MHRA and the HRA, to rebuild capacity and deliver on reduced turnaround time for all approvals

The Spring Budget 2023 announcements on medicine regulation and MHRA funding were encouraging and will help to rebuild the UK's reputation in clinical research. However, these actions are not designed to tackle delays in the clinical trial approval process or deliver world-leading performance.

To do so, HM Treasury should provide further additional annual funding to rebuild MHRA capacity and expertise in clinical trials (and, where applicable, build additional HRA capacity) so that it can set and achieve more ambitious KPIs that would match those in Spain and other competitor countries. Additional resource for the MHRA should allow it to:

- develop effective partnerships and collaborations to benefit from the diversity of expertise and substantial experience in the wider clinical trials community (including those who design, conduct or participate in clinical trials)
- adopt Good Clinical Trials Collaborative's principles for good randomised trials: the Good Clinical Trials Collaborative has already produced The Guidance for Good Randomized Clinical Trials (https://www.goodtrials.org/) with input from a wide variety of stakeholders, including regulators, funders, academic trialists, industry, professions and public, from around the world. The MHRA would benefit from adopting and implementing these principles – to foster innovation

and flexibility in order to deliver reliable results efficiently and in a way that involves patients as partners

- provide training and skills development to manage the increased use of risk-proportionate and innovative methods which provide new challenges for regulatory staff. Such staff will need to develop and maintain skills in novel methods underpinned by a thorough understanding of the scientific principles of clinical trials. In addition to taught courses and continuing professional development activities, there could be significant benefits from secondments both into and out of the agency. This could include placements with large MRC or NIHR-funded academic trials units
- ongoing improvements based on inviting feedback from those who interact with the MHRA across all steps of the clinical trial life cycle. Such a process would not only inform service improvement, such as, for example, timeliness and clarity of processes, but would help identify needs for training, skills development and co-development of guidance documents

Similarly, to achieve more ambitious KPIs across an expanded number of trials, the HRA needs additional annual funding rather than the current proposed reductions. Although the HRA has continued to meet targets for turnaround time for approval, it has made ongoing efficiency savings and would likely need more funding to match the increased clinical trial activity required by the ambitions of this review.

Recommendation 4: a comprehensive and mandatory national approach to costing and contracting should be developed and instigated, in partnership with industry

To deliver dramatically quicker approval times we need to address the obstructive, time-consuming and duplicative bureaucracy that prevents NHS providers and clinicians from undertaking commercial research. Achieving this goal requires a truly comprehensive national approach to contracting. By radically expanding the NCVR, the government should establish a working group, led by the HRA and consisting of industry, NIHR and its equivalents, the NHS and the life sciences industry during 2023 to agree and expand on the national commercial clinical trials contracting documents.

The group should cover, as far as possible, all relevant aspects of trial set-up and approval that can be harmonised, including information governance, pharmacy review and pathology and radiology reviews. The framework should cover all trial settings, not just hospital-based trials, and should be extended to all technology types such as digital therapeutics or advanced therapy medicinal products.

To be successful, the new approach needs to be both mandatory and enforced, unlike the existing NCVR protocols. This can be achieved through:

- an extension of existing indemnity arrangements to cover all risks associated with operating clinical trials, removing any justification for trial sites to carry out their own compliance checks, so that there is a single set-up process led by a trial's lead site. These indemnity arrangements should include agreement with relevant bodies that regulatory action will not be taken against the NHS where it

has acted in good faith in taking assurance and advice from regulators and in following the national contract framework

- an agreement between the NHS and industry, which could be agreed under the new pricing scheme with industry due to come into force in January 2024, to make the use of national contracts compulsory for companies. NHS organisations refusing to use national templates or imposing their own additional burdens, could lose access to NIHR funding

The goal is that, by 2025, all trials in the UK should be subject to a common approvals process that requires no parallel processes to be operated, with a single centralised process, which could be led by the HRA and the MHRA, to review all relevant approval documentation and providing confirmation of compliance that is automatically accepted by all participating sites.

Problem statement 2: lack of transparency and data about commercial clinical trials activity in the UK

There does not seem to exist a consolidated real-time view about which clinical trial sites are carrying out which kinds of trials for what number of patients, and whether they are performing against the targets agreed with their commercial and other partners. If this is true of research into medicines it is even more true of research into devices, diagnostics and the rapidly growing digital health sector. It is not acceptable that we are spending hundreds of millions of pounds each year and cannot properly account for whether it is delivering excellence or not.

The lack of good-quality data has 3 negative consequences. First, it means that very little performance management is possible by the funders of the research infrastructure, such as NIHR. As a result, underperformance goes unchallenged and over-performance unrewarded. Second, it means that industry has no way of seeing which trial sites are performing well or have capacity, and which should be avoided. Too often they are selecting sites in the dark, especially small biotech or healthtech companies with less experience of working in the UK or outsourcing these decisions to clinical research organisations. Third, it means that clinicians, patients and the public are not able to find out which trials are recruiting in their area or virtually that might be relevant to them.

Recommended significant actions

Recommendation 5: The MHRA, the HRA, NIHR and its equivalent organisations across the UK should collect, consolidate and publish national monthly returns on all the clinical trials activity that is happening in the NHS, and NHS bodies and commercial sponsors should publish numbers of patients in trials on a monthly basis

Real time data should be collected, consolidated and published for all trials regardless of how they are funded or in which settings they take place. This central portfolio management system should be procured UK-wide and presented publicly

on a monthly basis via a single dashboard of clinical trial activity. The open competition to designate hosts of the NIHR regional research delivery networks (RRDNs) in England should be used as an opportunity to strengthen accountability for performance.

The transition of the NIHR CRN during 2023 to create the new Research Delivery Network (RDN) provides an opportunity to radically improve reporting and transparency. As well as recording clinical trial activity, this could also capture financial information, including income generated from commercial trials to raise the profile of the financial benefits of clinical trials. Alongside this, common standards should be introduced for coding patients in clinical trials, which could then be uploaded onto electronic health records (EHRs) and accessed by leaders (such as in NIHR) to monitor performance, capturing all enrolled patients. This would overcome existing issues with SNOMED (the structured clinical vocabulary used in EHRs), which currently does not allow for all patients in a clinical trial of a new treatment to be recorded.

Recommendation 6: building on near real-time activity and performance generated according to the above recommendation, the UK governments should create a UK phase 1 to 4 clinical trial directory – called 'clinicaltrials.gov.uk' – to create a single source of activity for patients, clinicians, researchers and potential trial sponsors

There is no single directory of clinical trials in the UK; data on clinical trials activity is held by the NIHR CRN, and in some cases published. ISRCTN is part of the World Health Organisation Registry Network, and UK researchers can register their trials on the site. Originally, ISRCTN stood for 'International Standard Randomised Controlled Trial Number'; however, over the years, the scope of the registry has widened beyond randomised controlled trials (https://www.isrctn.com/page/about).

The US clinicaltrials.gov (https://clinicaltrials.gov/) site holds some information about UK trials, but it is not comprehensive or up-to-date. It is a condition of getting REC approval that clinical trials are registered, ideally before the first participant is recruited and no later than 6 weeks after the first participant is recruited. Trials are registered on either the clinicaltrials.gov or ISRCTN sites, and this information is fed into the NIHR Be Part of Research site. The lack of a single source of planned and ongoing trials leads to inequity of information, and senior clinical academics are more likely to refer patients to trials that they are aware of through their research practice and missed recruitment. A clinical trial directory would help trial recruitment if this directory:

- maintained up-to-date information for phase 1 to 4 trials in the UK, including status of trial (open, closed, recruiting, and so on) to enable capacity planning
- contained full inclusion criteria, including gene and variant level inclusion and exclusion criteria
- included a machine-readable interface, integrated with clinical decision support systems, ensuring patient-to-trial matching was integrated into clinical care

Problem statement 3: lack of accountability at every level for underperformance in clinical trials

Underpinned by the absence of good-quality, near real-time data, there is a lack of accountability for NHS organisations about their performance in delivering clinical trials. Trusts, R&D departments, NIHR CRNs and others do not appear to suffer the consequences of poor delivery, nor do exceptional performers receive additional investment to grow their activity. This means mediocrity goes unchecked despite the fact that all NHS bodies are under a legal duty to promote research.

Adding to this lack of accountability is the absence of agreed KPIs that all partners in the clinical trials sector are measured by, and held accountable to, in return for taxpayer funding. On one level there is a proliferation of KPIs and endpoints for specific trials; on the other, there is no set of agreed high-level KPIs, publicly reported on, by which to judge performance of the system as a whole and individual NHS trial sites in particular. Coming to a judgement about how well a trial site is doing, and then holding those responsible accountable, is therefore extremely challenging.

As well as improving the measurement of inputs, including number of trials, and participants enrolled, participant retention, it is important to measure the impact of clinical trials. For example, that trials allow the use of the most innovative products for diagnosing and treating UK patients.

Recommended significant actions

Recommendation 7: DHSC, DSIT and the NHS should set stretching annual targets for increasing commercial trials in the 4 countries of the UK and carry out annual benchmarking exercises comparing performance against competitor countries. Central to this ambition should be the objective of doubling recruitment to commercial clinical trials within the next 2 years, with a further doubling by 2027

The letter from DHSC and NHSE on 13 March 2023 exemplifies the lack of accountability for underperformance that exists in the system. The letter rightly points out that set-up and patient recruitment times for commercial research are recovering more slowly than for academic trials, and asks trusts and sites to, in effect, ‘use it or lose it’. But there are no policy levers to enforce this request and there will be few, if any, consequences for sites that continue to underdeliver.

To correct this, sites which continually underdeliver against local and national targets should relinquish NIHR and other funding they get to enable clinical trials, with that funding distributed to higher-performing sites. The funding formula that is distributed to NHS trusts and primary care settings should include specific elements that reflect performance against the KPIs for commercial research listed above, with funding being redistributed to those that achieve their goals and away from those that do not.

Under their legal duty to promote research, each integrated care board (ICB) and health board should put in place research strategies and report on commercial research activity in their system through system-wide dashboards. CQC inspections should be strengthened so that above benchmark and increasing levels of research activity are a mandatory part of achieving an 'outstanding' rating in the well-led framework.

The open competition to designate hosts of NIHR RRDNs in England should be used as an opportunity to strengthen accountability for performance. In the short-term, with the transition of the CRNs during 2023 to create the new RDN (https://www.nihr.ac.uk/explore-nihr/support/clinical-research-network.htm), a new approach to performance management should be introduced that rewards and increases funding to sites that perform highly against the core KPIs and reduces or ceases investment in those that do not. Low-performing sites should be obliged to change leadership or relinquish funding towards better-performing networks. The RRDN leads, which 'host' and co-ordinate the network, should be responsible for holding sites to account for performance, and in turn be accountable for the performance at a regional level.

Recommendation 8: a new UK-wide set of KPIs for clinical trials should be established covering all critical aspects of the set-up, approval of and recruitment to trials, an overall measure for UK performance in clinical trials, and outcome measures for the impact of commercial trials. These KPIs should apply to all bodies involved benchmarked against global exemplars

The metrics should provide an effective means of monitoring the performance of the UK in clinical trials, and should provide a measure of: the competitiveness of the planning, approvals, and set-up of trials; the overall environment measured by commercial trial activity; and the impact of commercial trials. Delivery partners across the UK should work together and with industry to design a set of metrics to be tracked to monitor delivery on the targets set out below and to provide clear accountability at every contributing level of the system.

Planning approvals and set-up

- overall metric: time from application to a regulatory authority to the first patient's first visit, with a goal of reducing the UK's time to under 200 days, as seen in other countries, such as the USA, Spain and Australia (https://www.gov.uk/government/publications/life-science-sector-data-2022)

Overall UK trial environment

- overall metric: UK recruitment to commercial clinical trials, with a goal of doubling this within 2 years and then again by 2027

Impact of commercial trials

- income to the NHS from commercial trials

- economic contribution of commercial clinical trials
- scoping of measures of adoption of new products in the NHS

Recommendation 9: in England, a new operating model for the NIHR CRN should be introduced to strengthen accountability and delivery

As it transitions away from the CRN in 2023, NIHR should spin out the RDN as a government company owned by DHSC, along the lines of Genomics England. It should be given an independent board and leadership, objective KPIs and performance incentives, with funding linked to achieving agreed outcomes. The new, independent CRN would be commissioned by NIHR on a 5-year basis to deliver a set of stretching objectives that would place the UK among the globally competitive countries for delivering clinical trials. Among others, these objectives should include ambitious year-on-year increases, such as 50%, in commercial trial activity. The new CRN would then commission the individual regional or disease specific CRNs on a similar competitive basis.

Problem statement 4: research is not systematically prioritised by or within the NHS

Researchers, whether they are academic, part of the NHS or in industry, do not feel that research is a priority for either the NHS or the wider UK economy. Duties in law (for England, in the Health and Care Act 2022 (https://www.legislation.gov.uk/ukpga/2022/31/contents/enacted), for example) to promote more research in the NHS, including clinical trial activity, are relatively weak and hard to enforce, and there is little good data on R&D activity or relevant performance targets for NHS bodies at any level. Commitments to improve research and innovation barely featured in the NHSE's 2018 Long Term Plan.

At a local level, CEOs were not felt to prioritise research activity and directors of R&D at NHS organisations were not felt to prioritise commercial research activity. Furthermore, there is not enough of a 'business development' mindset and NHS R&D services – which are intended to carry out this function – are under-powered. The guidance for ICSs published in March (https://www.england.nhs.uk/long-read/maximising-the-benefits-of-research/) provides more detail on the expectations for how ICBs will meet their duties (in the Health and Care Act 2022) to facilitate and promote research, by setting out best practice.

The NHS priorities and operational planning guidance for 2023 to 2024 (https://www.england.nhs.uk/publication/2023-24-priorities-and-operational-planning-guidance/) makes mention of research, and says that 'improving NHS patient care, outcomes and experience can only be achieved by embedding innovation and research in everyday practice', referencing the ICB duties, but research is not included as part of the top priorities referenced in the document.

This is a significant missed opportunity and a failure to harness the desire of clinicians to take part in research. The Royal College of Physicians has found that 57% of doctors want to participate in research, and 53% of respondents to a

survey of NHS staff cited a lack of time as the biggest barrier to research participation (https://www.rcplondon.ac.uk/projects/outputs/research-all-analysis-clinical-participation-research), alongside funding and a perceived lack of skills and supportive culture for research. Feedback from system leaders has supported this, demonstrating that protecting time for conducting research, though vital, is not enough. We also need to make sure that the infrastructure is in place to conduct research; that there is sufficient portfolio of research to ensure continuity for clinicians; and that we better recognise the value of research to patient care.

Currently, although there are efforts to protect time for research, it is not communicated effectively as a core component of delivering high-quality clinical care, despite the compelling evidence that research is itself a valuable and vital component of continuously improving care for NHS patients. According to a Cancer Research UK survey conducted before the COVID-19 pandemic (PDF, 2,841 KB) (https://www.cancerresearchuk.org/sites/default/files/creating_time_for_research_february_2021_-_full_report-v2.pdf), 44% of NHS staff were unsure if research was a priority in their trust or health board's clinical strategy, resulting in a leadership gap that contributes to low awareness of clinical research's positive impact on patients, staff and NHS finances.

Stakeholders to this review have cited a shortfall of research nurses, pharmacy and imaging resources, and aseptic teams as constraints to delivery of clinical trials. The forthcoming long-term workforce plan needs to ensure the NHS has the requisite workforce capacity and capability for research.

Case study: London North West University Healthcare Trust

At London North West University Healthcare Trust, host trust of St Mark's Hospital, a specialist bowel hospital, there was no ophthalmology portfolio research until 2017 when an ophthalmology consultant with research interest was appointed and allowed to convert one clinic session to a dedicated research session. The emphasis was to focus on commercial trials, to generate income to fund research delivery support. In the 5 years since, this session has facilitated 11 commercial trials and well over £1 million income to the trust. For 5 of those trials, the site has been the top site recruiting in the country with overall recruitment of over 200% of the target recruitment.

Recommended significant actions

Recommendation 10: a statement should be made by the NHS leadership and ministers of the UK's intention for the health service to be the world's leading platform for health R&D, and annual R&D targets should be introduced for the NHS at every level

A clear statement is needed from senior leaders that research is integral to care and should be prioritised accordingly in the NHS. To bolster this statement, clear metrics of performance should be developed and reported on. To be effective, this prioritisation of research needs to flow down into the system. This should include the creation of R&D leads at ICS and health board level, where they do not currently exist, to implement system-wide research strategies and to hold account NHS providers for their performance in clinical trial activity. In England, this would provide the leadership required for ICSs to fulfil the statutory duty to promote research given to them in the Health and Care Act 2022.

The NHS should be obliged to systematically collect and publish data on research, development and innovation activity in the NHS each year, with an annual R&D target for the NHS in the annual mandate and annual reporting to Parliament against that ambition.

These data collections and R&D targets should apply to all levels of the NHS, at national, regional and trust levels. As set out above, a system-wide dashboard should be developed to report on performance in delivering commercial trials. The research guidance for ICBs recommends that they develop a research strategy, yet it is clear from input to the review that there is variation across ICS areas in level of research activity and expertise (https://www.england.nhs.uk/long-read/maximising-the-benefits-of-research/).

It would therefore be helpful for ICSs to discuss and share expertise and best practice in research to inform the development of these strategies both with each other and with industry leads, which could be facilitated at a national level by the Academic Health Science Networks (AHSNs). Within trusts, CEOs must be made directly responsible for trial delivery and the creation of a clinical environment which facilitates trial recruitment.

Recommendation 11: the business development services in NIHR and its equivalent bodies should be set explicit performance targets to increase the number, kind and diversity of commercial trials

A ramp-up was achieved previously between 2012 and 2016 and should be targeted in the coming years. Existing funding should be redirected into these services and a clearer link established between these services at UK level and OLS and the Life Science Office in the Department of Business and Trade (DBT) to deliver a concerted and ongoing global marketing exercise to draw more commercial research funding in the UK.

The NIHR CRN has always had high level objectives (HLOs) to measure delivery of its key objectives, as part of the contractual arrangements for the LCRNs and the national CRN Coordinating Centre (https://www.nihr.ac.uk/documents/nihr-clinical-research-network-high-level-objectives-outturn-report-202122/31638).

Problem statement 5: doctors, nurses and NHS organisations lack incentives to take part in research,

especially when it is commercially funded

One reason that the accountability problem is not pursued is that setting up commercial trials is often seen as too onerous, or at best a sideline to the delivery of healthcare, rather than both a clinical and societal good and a source of additional income and resource for a hospital or GP provider. Income generated from commercial trials is too often lost in the system. There is a lack of incentives, both financial and professional, for researchers to take part in commercial research compared to academic studies, and we do not appear to systematise or reward excellence in this field.

Participating in non-commercial research is of value to clinicians, particularly academic clinicians, due to the opportunities to collaborate and get recognition and scientific credibility, for example via publication in academic literature. Participation in commercial research does not tend to be recognised academically or in clinical impact awards, and in many trusts does not directly translate into funding to support a clinician's own further research. Many clinicians personally spend time putting arrangements in place for non-commercial research, negotiating between departments and advocating for the study.

In many other countries, clinicians participating in commercial trials have support staff who provide a service for the companies, 'hiding the wiring' of the internal arrangements to set research up. In the absence of sufficient financial support, commercial clinical trials in the UK do not have advocates within participating NHS trusts. This means that commercial sponsors and contract research organisations must directly interact with staff, often liaising directly with different structures and roles across the NHS. This is a considerable contribution to the complexity and burden for commercial research in the UK.

There is a direct financial gain for the NHS in conducting commercial research, which should then lead to provision of additional capacity to improve care. However, feedback from NHS organisations and commercial sponsors of trials demonstrates that, in some cases, NHS sites do not invoice commercial sponsors and therefore do not receive payment, and even when payment is made there is no transparency about how this income is re-invested within the NHS.

A significant amount of income is generated for NHS trusts by taking part in commercial trials, estimated at £355 million in 2018 to 2019 (https://www.abpi.org.uk/r-d-manufacturing/clinical-research/an-opportunity-for-growth-clinical-research-in-the-uk/). Although there is work in progress to ensure this income is reinvested into improving capacity to do research, more could be done to ensure that the value of the income is most effectively captured. There is an opportunity to better use income generated by industry trials to help NHS research become more self-sufficient. For example, income could be used to support local research infrastructure and improve sites' recruitment and retention of high-quality academic clinicians, in turn, attracting further industry investment.

However, as evidenced by a submission to the review, research delivery teams are often unsure how much research revenue will be reinvested into research capacity. Stakeholders have provided examples of financial incentives used in other

countries, for example in the USA where clinicians receive income directly for referring patients to clinical trials. It should be recognised that, alongside commercial income for trials, there is a substantial amount of money spent on clinical trials in the NHS as the NIHR CRN has £350 million of funding per annum.

Recommended significant actions

Recommendation 12: income generated by commercial sponsors should be explicitly directed to units and departments leading trials in NHS sites to provide direct financial incentives to take part in commercial trials

Giving doctors, nurses and other staff more time to take part in research is clearly desirable, not least in providing greater job satisfaction for those staff themselves. In theory, time is protected under current contracts for this activity but, in reality, it is under pressure from frontline responsibilities. There is no easy fix for this that does not require significant extra funding, which may be unrealistic in the current fiscal environment. However, this problem could be addressed by ensuring that income generated by running commercial trials is reinvested in a transparent and visible way to those leading the research in NHS sites. As a simple guide, the benefits that accrue from commercial trials should be:

- accounted for in trust and NIHR CRN annual financial reports
- transparently distributed on a 40-40-20 basis between the units delivering commercial trials (for example, putting the funding into a ‘principle investigator box’ – assigning funding to principal investigators (PIs) for trials, for spending on more nurses, training and other infrastructure within their department), the trusts themselves, so that there is a clear financial incentive to do more trial work, and regional CRNs. NIHR CRNs should receive further financial incentives from NIHR for successfully delivered trials

The criteria by which Clinical Impact Awards (https://www.gov.uk/government/publications/national-clinical-impact-awards-resources-for-applicants-and-employers) are distributed should also be reviewed, so that they genuinely promote excellence, rather than simply providing cross-subsidy to trusts to free up clinical time to focus on research, regardless of the quality or impact of that research. The awards should recognise and reward commercial activity as well as non-commercial trials and be accessible to clinicians in primary care and other settings, as well as those working in hospitals.

Recommendation 13: the NHS should use the upcoming NHS Long Term Workforce Plan and UK RRG Research Workforce Strategy to establish a clinical trials career path for training critical roles for research

This should include clinical research nurses, managers, informaticians and managers, with specific commitments to increase numbers of pharmacists and research-trained nurses in both primary and secondary care settings over time, which could also be measured as a proportion of the whole NHS workforce. As highlighted by the House of Lords report on clinical research

(https://committees.parliament.uk/committee/193/science-and-technology-committee-lords/news/175630/the-future-of-clinical-research-in-the-nhs-is-under-threat/), large numbers of PIs are due to reach retirement age soon. Workforce strategies should, therefore, contain properly funded plans for maintaining and increasing this network of experts across the NHS. NHS bodies should publish as part of their annual report the number of research-trained and research-active clinicians they employ.

As part of this workforce effort, there should be dedicated professional recognition for outstanding clinical trial delivery. This could take the form of the Academy of Medical Royal Colleges and the funders of clinical research in the UK establishing a new Academy of Clinical Trials to raise the profile of the sector and provide fellowships and other opportunities for professional development and recognition.

All GPs should be able to apply for Clinical Impact Awards, which are currently only open to academic GPs. The Academy of Clinical Trials should also deliver an accreditation service to recognise excellence at NHS provider level through a Trial Excellence kitemark.

Problem statement 6: conversations about research are absent from many interactions between clinicians and patients. The topic has a low profile with the public, especially among disadvantaged or marginalised groups

Despite our excellent medical research charities, there is too little focus on the value of clinical trials to patients, the NHS and wider economy. We are at risk of squandering the opportunity provided by COVID-19, when medical research was at the fore, and the idea that access to clinical trials should be a right of patients as part of 'standard of care' does not appear to have been embedded in NHS practices or professional guidelines. This leads to a patient population who are not engaged enough in research and not aware that taking part in research could benefit their care.

Furthermore, it is essential that clinical trials in the UK reflect our diverse population to provide benefits to all patients. While NIHR has published a welcome report on analysis into the diversity of research participants, regular and further monitoring of inequalities in patient participation of clinical trials should be implemented to ensure there is equal access across all parts of the population (https://www.medcityhq.com/2023/03/29/why-diversity-in-clinical-trials-is-essential-to-the-future-of-uk-life-sciences/). The population diversity of the UK offers the potential for companies to demonstrate the effectiveness of products across a wide range of patient populations.

There is work underway to establish principles for how the diversity of patients recruited to research can be improved. This includes the guidance published by NHSE (https://www.england.nhs.uk/aac/publication/increasing-diversity-in-research-participation/) to 'provide practical insights for researchers on how to engage more diverse participants in health research'. The guidance highlights that NIHR data

shows that UK geographies with the highest burden of disease also have the lowest number of patients taking part in research, and suggests ways of improving this for individual trials across planning, delivery and follow-up by considering the barriers to engaging with and taking part in research. Successes in engaging patients in research can be seen across medical research charities working with patient groups, specialist hospitals promoting trials to specific cohorts of patients, and the programme to rapidly enrol participants in studies for COVID-19 vaccines. These approaches should be expanded and built upon.

Site selection is driven by a number of factors, including the research design, its complexity and facilities and resources needed to deliver it. The NIHR CRN supports companies to plan, place and perform their research in health and care services, including sharing data, for example, on areas of health need. The final decision on placing a study rests with the sponsor, or the clinical research organisation where they are managing the study on behalf of the sponsor. Whilst the NIHR CRN aims to inform this decision, it is not mandatory for sponsors to follow the advice.

The lack of a single source of truth about clinical trials activity in the UK makes it even harder for clinicians, patients and the public to know what is available, and too often people hear about potential trials though word-of-mouth or closed networks. Compared to the opportunity to donate blood or organs, for example, the opportunity to take part in research is hidden.

Another important aspect of involving people in research is the visibility for researchers of people who may be prospectively interested in being involved in research programmes. NIHR has developed Be Part of Research, which is now linked within the NHS App in England, and could be further integrated and expanded. Input to the review has included a suggestion that Be Part of Research could be further developed, including to help patients to see the impact of trials. This could be by including examples of completed trials and what the process of taking part involved and how it changed patient care.

Recommended significant actions

Recommendation 14: an ongoing public campaign should be conducted to promote research and to generate evidence on the most effective communication methods, in partnership with medical and research charities

This campaign could build on previous examples that have successfully generated public support for research, for example, during the COVID-19 vaccine trials, GRAIL's Galleri study or the creation of UK Biobank. There is little evidence of the effectiveness of different methods of engaging the public with research, and an effective campaign would, therefore, include pilots, or other testing, to understand what methods are most effective across different communities in the UK.

The campaign should be funded and delivered in partnership with industry and medical research charities. Asthma + Lung UK has argued convincingly that the combination of medical research charities and companies are best placed in the

health landscape to lead a conversation with the public and patients about the importance of taking part in clinical research (https://www.blog.asthmaandlung.org.uk/blog/clinical-trial-recruitment-asthma-lung-uks-proposed-solution). A particular focus of the campaign should be increasing the number of people from disadvantaged communities who are part of the UK's health research networks.

Recommendation 15: full Integration of NIHR Be Part of Research with the NHS App should be accelerated, with enhanced opportunities to take part in clinical trials added to the platform.

There needs to be an effective route into research for the public, so that people can indicate their interest in taking part in current or future studies. NIHR and NHSE are developing the integration of Be Part of Research with the NHS App, which could provide an excellent tool for people to easily register their interest, and there is now a link within the NHS App. This is currently a simple referral to an external website but should become an embedded part of the NHS App so that the public can choose to be part of this, or any other relevant medical research cohort, registry or other regulated patient recruitment database operated in the UK from within the NHS App itself, where that is the best route for patient engagement.

In addition, this improved functionality should give patients the opportunity to have their health data proactively analysed by an NHS research partner to see whether they are suitable for an interventional clinical trial. Initially this should operate as an opt-in system, but subject to a rigorous patient and public deliberation exercise this could evolve into an opt-out system, as is the case with organ donations.

Alongside this work to develop the NHS App, consideration should be given to other digital and non-digital channels, and equivalents in Wales, Scotland and Northern Ireland, to ensure maximum reach across a representative population. Patients could be given a set of choices of how they engage with research, which takes into account their choices around the use of data and participation in trials. These choices might include:

- not at all (this is, in effect, the national opt-out)
- their data being used as part of a general cohort for observational or retrospective studies, but not actively used in a specific interventional study (the current status of people who do not choose to exercise the national data opt-out)
- being offered the opportunity to be part of a specific interventional study that could directly impact their care and health outcomes

It is important to note that the purpose of these changes is to enable people to be approached to take part in clinical research that is relevant to their health needs, and that each individual would always be free to refuse to participate.

As well as developing its own cohort of research-ready patients, the Be Part of Research programme should develop a national registry network from the broad ecosystem of existing disease and other registries in the UK. Be Part of Research can act as the centrepiece of UK trial registries, pooling much of the registration

capacity, some of which can come from direct linkage with other registries – which NHSE is already scoping. Be Part of Research can be a promotional beacon for industry as well as a focal point for increasing public engagement. This service should be available to patients via the NHS App, as well as other routes.

Recommendation 16: the government and the NHS should work with royal colleges and unions to integrate 'research conversations' into all NHS communications and clinical interactions

Royal colleges and unions are well placed to develop resources to support clinicians and other healthcare staff to engage with research, and in turn to effectively engage with patients about research opportunities as part of their care. These measures should build on the above recommendations to ensure that research is systemically prioritised by the NHS and other organisations, and that steps are taken to ensure clinicians have time to engage with research.

Recommendation 17: specific targets should be introduced for the new RDN co-ordinating centre and regional centres to expand research to multiple sites, and to increase diversity of patients recruited

Although there is an overall ambition to develop 'hub and spoke' models for running trials, in reality, much research activity is currently focused on a select number of 'hubs', often university hospitals, with the 'spokes' of district general hospitals (DGHs) and similar being second order, despite the fact they often serve more disadvantaged communities where the disease burden is highest. As the CRNs, as re-commissioned this year, they should be given specific performance targets on both expanding research into these 'spoke' centres and increase the diversity, including gender, geographic, ethnicity and age, of patient recruitment into trials.

Problem statement 7: we are failing to take advantage of the NHS's considerable data assets

The UK is not making the most of its extraordinary data assets. We are also in danger of talking up our advantages in this area to life sciences companies while underdelivering in reality. This finds expression in 2 problems:

- we are not systematically using our proliferation of databases, registries, cohorts and EHRs to proactively identify, stratify and approach potential clinical trial candidates without them having already been given consent to be approached. This Catch-22 denies patients the chance to take part in research that could improve their health
- once patients are on trials, we are not able to ensure that all relevant data covered by that patient's clinical trial consent, wherever it might sit in the NHS, can be joined up and analysed as part of that trial. There are some technical barriers around compatibility, common standards and interoperability that need addressing, but just as important is the absence of clear guidance about what is permissible and desirable under current data protection and other relevant law

The Clinical Practice Research Datalink (CPRD) Speedy Patient Recruitment Into Trials (SPRINT) (https://cprd.com/cprd-sprint-speedy-patient-recruitment-trials) initiative has been developed to support the recruitment of patients into commercial clinical trials. This initiative uses the CPRD platform, which enables GPs to provide patient data to a primary care database, which covers 16 million patients in the UK. An anonymised search is carried out on this database to: provide rapid feasibility assessments for sponsors; advise on optimum site location; and provide GPs with a list of potential patients to be invited to take part in trials. The patients received invitations from their GPs but not directly, and while a very important programme, CPRD only covers around one-quarter of the population.

There is also in place the NHS DigiTrials (https://digital.nhs.uk/services/nhs-digitrials) service to recruit patients, which provides services in:

- feasibility – using routinely collected NHS data to provide an assessment of how many patients meet the criteria for a trial and where they are located
- patient recruitment – which is currently being piloted
- communication with patients during trials
- follow-up monitoring of patient outcomes

These 2 programmes both provide benefits to clinical trials in the UK. However, they do not constitute a comprehensive coverage of patient data access and are limited in scope (CPRD SPRINT has access to primary care data where GP practices have signed up, and NHS DigiTrials has national coverage of select secondary care data in England). The optimum approach, to enable clinical trial recruitment, would be to have one single view of patients across different care settings.

Recommended significant actions

Recommendation 18: agencies responsible for information governance within clinical trials should establish a common approach to contacting patients about research within the current legislative framework

Proactive contacting: the HRA and other agency guidance needs to change to allow research teams to contact patients based on EHRs, databases and registries to ask if they would like to take part in research. NHS DigiTrials is leading the way here: its new directions pilot has enabled NHSE to test the concept of the NHS DigiTrials Recruitment Support Service by using it for real trials (https://digital.nhs.uk/about-nhs-digital/corporate-information-and-documents/directions-and-data-provision-notices/secretary-of-state-directions/pilot-nhs-digitrials-recruitment-support-services-directions-2021), establishing appropriate mechanisms to avoid the ‘consent to contact’ trap and allow prospective recruitment based on section 251 support.

This approach needs to be rolled out beyond the data which is held by NHSE itself and applied to all other relevant health data repositories in the UK, with a task and finish group established to report within 3 months on how a common approach to ‘finding, following and recruiting’ patients can be achieved within the current

regulatory framework. The group should include the HRA, the NHSE Centre for Improving Data Collaboration (CIDC), the National Data Guardian (NDG) and ICO, as a minimum, and aim to create template guidance on information governance that can be part of the national framework proposed above.

Recommendation 19: all patients receiving genomic testing of any kind in the NHS should be offered a standard consent for engaging in research

Research consent should be routinely captured for all genetically sequenced patients, not just those receiving whole genome sequences. This consent should allow relevant data to be made securely available for approved research. The majority of cancer and rare disease patients in the UK are not yet offered research consent, which means they do not enter databases as a potential resource for clinical trial recruitment or other clinical research activities (including functional genomic research). Because this is an emerging field, those who do not have the opportunity to consent are likely to miss out on results that come from research interrogation of their genetics that could have important clinical consequences.

Recommendation 20: a national participatory process should be conducted to examine how to achieve greater data usage for clinical studies in a way that commands public trust. This should seek to establish a publicly supported position around the proactive contacting of patients to take part in clinical trials and studies that could form part of their care

Driven and overseen by a participative process like that carried out by Genomics England or ONE London, clarity about the requirement for data controllers to respect explicit consent provided for REC-approved clinical studies would allow relevant health and wider data for patients engaged in a clinical trial to be used as needed for that research. All relevant data controllers would be obliged to comply with this instruction. This would overcome the current problem where individual data controllers can make decisions about how to share data and its subsequent uses, causing blockages in the flow of data for research even after a patient has given explicit consent.

Beyond this, a more radical approach is required that would involve redefining ‘standard of care’ to include allowing patients to be proactively approached to take part in studies. Alongside, or as part of the participatory process on data usage, the royal colleges, NHS leaders, patients and charities should engage with patients and the public to make recommendations on how this can be achieved legally and ethically, with the goal that research organisations, including universities, NHS bodies and industry, would be allowed to analyse the range of existing datasets, where lawful and in line with policy, including that arising from the Data Saves Lives strategy, to identify and approach suitable patients to take part in research without having to seek ‘consent to contact’. At the same time, patients who do not want to be approached should be given the opportunity to opt out.

Recommendation 21: the NHSE Data for R&D Programme’s NHS Research Secure Data Environments (SDEs) Network should be rolled out, including

urgent publication of guidance for NHS bodies on engaging in research with industry

The data for the R&D SDE programme needs to proceed because it will help provide the data infrastructure required to underpin the reporting, data linkage and other services necessary to deliver improved clinical trial services in England. One specific focus for country-level and cross-UK improved data infrastructure should be improving the timeliness and completeness of disease registries. Registries like those provided by the National Cancer Registration and Analysis Service (NCRAS) are rich sources for commercial and academic trialists to plan trials and recruit patients. However, the utility of these registries would be vastly improved if:

- registries linked to near real time clinical data (in other words, refreshed weekly) refreshed from hospital clinical systems
- registries linked to genotypic and variant level information, increasingly relevant for molecularly stratified clinical trial selection criteria
- they contained consent information, stating whether patients are already consented re-contacted via their clinical teams

As the national and sub-national SDEs are further developed, the NHS's Centre for Improving Data Collaboration must urgently publish its guidance to NHS bodies on appropriate forms of value-sharing when those bodies engage with the private sector to carry out data-rich research. The absence of clear guidance is holding back potential collaborations that would command the support of the public and deliver benefits to patients, the NHS and industry alike.

To unlock the potential within our health data assets, we need a scalable centralised national real world data recruitment service which encompasses data from multiple care settings, delivers to industry timelines and interfaces seamlessly with our clinical trials delivery infrastructure. This needs to build on the ongoing efforts of the NHSE Data for R&D Programme.

Problem statement 8: primary care is a negligible provider of clinical trial activity, despite the opportunities it provides for delivering population-scale trials, and there is too much reliance on hospital settings for the delivery of trials

Transforming this sector is not just about doing 'standard' trials well but it is also about embracing the opportunities for innovation. This could be by siting more research in primary care or having a proactive regulatory system for decentralised trials. In other countries, regulators are recognising the importance of these new approaches to trials - for example, the FDA in the USA has now issued draft guidance on the use of decentralised trials (https://pharmaphorum.com/news/fda-sets-out-its-thinking-decentralised-clinical-trials).

As it stands, only around 10% of clinical research activity (as measured by the number of participants) takes place in primary care despite the potential of this area, and around 4% of practices are recruiting patients to commercial trials. As

demonstrated in the Salford Lung Study and PANORAMIC trial (see case study below), primary care has the potential to deliver large-scale trials using innovative methods at a fraction of the usual cost.

Case study: PANORAMIC trial

PANORAMIC is a UK-wide clinical study, sponsored by the University of Oxford and funded by the NIHR, to find out which new antiviral treatments for COVID-19 in the community reduce the need for hospital admission and help patients get better sooner. The treatments investigated include molnupiravir and, currently, Paxlovid, and the usual standard of NHS care.

The study is open to patients experiencing COVID-19 symptoms within the last 5 days, have had a positive PCR or lateral flow test for COVID-19, are aged 50 or over, or aged 18 or over with a health condition with high-risk of serious illness from COVID-19. Volunteers do not need to be vaccinated to be considered eligible.

Patients can join the national study by signing up independently on the PANORAMIC website or by participating via GP practices using the NHS Digital Population Health platform, which selects patients potentially eligible to take part.

Volunteers can participate in the study remotely from their own homes anywhere in the UK, without needing to visit a clinic or hospital. Patients answer questions each day either online or by telephone (or both) with the study team. The study team supports patients throughout the trial.

As of 18 April 2023, over 27,000 volunteers have participated since the trial's launch in December 2021.

In December 2022, PANORAMIC found that molnupiravir, the first antiviral treatment to be tested, did not reduce hospitalisations or deaths among higher-risk vaccinated adults with COVID-19 in the community. However, the treatment was associated with a quicker recovery time, and reduced viral detection and load. Patients who received this treatment reported feeling better compared to those who received standard care, and once well, they more often stayed well.

Recommended significant actions

Recommendation 22: financial incentives should be introduced for GPs to take part in commercial trials

NIHR and equivalent funding in the devolved governments should be used to create a network of primary care clinical trial networks to enable new forms of trial activity that are closer to the patient and increase opportunities for marginalised

communities to take part in research. These should ideally align with, or expand upon, the CPRD database, which provides primary care data for research purposes. Primary care reimbursement regimes, such as the Quality and Outcomes Framework (QOF) in England, and similar systems elsewhere in the UK, should be used to provide financial incentives to GPs to take part in research activity.

Recommendation 23: new primary care research networks should be introduced to increase the proportion of commercial trials taking place in primary care and 'at home' settings

When undertaking the re-commissioning of the regional CRNs, NIHR and its equivalent bodies in the UK should hold a competition for the creation of a small number of primary care CRN pilot schemes. These would be open to applications from consortia led by GP federations and primary care networks, and should provide seed funding for the creation of clinical research platforms that are based out of hospitals in community and primary care settings. These would link up relevant delivery organisations, such as community pharmacies, diagnostic providers, logistic firms and virtual care providers. In the long run, the goal should be to create at least one primary care research network (PCRN) in every ICS or health board in the UK.

Recommendation 24: regulators should produce guidance to support and promote innovative and decentralised trials

The UK regulators should work with industry, academia and other experts to develop central guidance by the end of 2023 on carrying out decentralised trials, covering the approvals and set-up processes and which settings, such as, homes or pharmacies, as well as more traditional locations, can be included as trial sites, to promote decentralised and innovative trials. This should include agreement from regulators to promote decentralised trials, including by agreeing that data generated according to central guidance using decentralised trials can be used for regulatory approval, as well as guidance on the appropriate use of technology within decentralised trials to gather regulatory-grade data. The UK regulators must aim to at least keep pace with international bodies, such as the FDA and EMA, in supporting decentralised trials. In doing so, they must make sure that guidance in this area allows the UK to host decentralised trials that will generate regulatory quality data that is accepted by other stringent regulators.

There is work ongoing in NIHR to improve the understanding of the process of planning, setting up and running a trial in the NHS for industry and including innovative and decentralised trials. This includes work from the HRA to define the 'ideal path' that trials should take to navigate the approval, set-up and delivery process. This should be built on to develop a new simplified and clear process map.

Recommendation 25: the government and regulators should develop a strategy for the use of AI in clinical trial design and regulation

As part of its AI strategy, the government should promote the better use of AI in clinical trial design and delivery. This could include measures such as an the MHRA ‘sandbox’ to allow industry, NHS and academic partners to evaluate new approaches to clinical trials, for example as part of patient data collection and analysis and reporting on delivery of trials to deliver regulatory quality data within a streamlined process.

Part 3: transforming how the UK does clinical trials

Introduction

The proposals outlined in the previous section of this report are designed to deliver a significant improvement in the number and kind of clinical trials taking place in the UK, to provide a rising tide that lifts all boats and makes the UK an attractive, competitive place for industry to site clinical trials once again.

The value of achieving this objective should not be underestimated, but we should not limit ourselves to that ambition. For each step of establishing and running a clinical trial in the UK, the actions recommended so far in this report will improve the system for all trials; to truly transform performance a more innovative approach is required.

As should be evident from the many case studies in this report, we are genuinely capable of delivering global excellence. Indeed, unless we set this ambition then we will not remain a life sciences superpower and the UK’s health and wealth will suffer as a consequence. However, funding for clinical research is typically not well-aligned to the strategic priorities of either the Life Sciences Missions or the NHS major conditions and areas of unmet need. This means that the UK does not provide an ‘end-to-end’ offer to industry from bench to bedside in the areas of medicine of most importance to us as a country. The question, then, is how to take the excellence we see on occasion in commercial trials and turn it into a systematic transformation of the way we fund and carry out clinical research in the UK?

This is what the proposal for new CTANs outlined below aims to achieve. Such networks would establish a new ‘enhanced service’ for clinical trial activity to meet the strategic needs of our health and life sciences sectors, providing access to additional resources, expedited approvals processes and other benefits. Each CTAN would be a joint venture between private, public, academic and charitable sector organisations of all sizes. It would use the strengths of small- and medium-size life sciences companies, and provide an exemplar for how, over time, all clinical research should be delivered. Establishing and then rolling out CTANs across multiple disease, therapeutic modalities and other fields would allow the NHS and other partners to prove that we are capable of delivering best-in-class performance as a rule, not an exception. CTANs should aim to build on, and improve, infrastructure already in place.

The Vaccines Innovation Pathway, the ACT platform (see case study below) and Brain Cancer Mission provide potential models for the service to follow, and demonstrate the benefits of highly innovative trial models, as does Protas - born out of the experience of running the RECOVERY COVID-19 trial, it provides a platform for large population health studies that is radically more cost-effective than the traditional trial model (see case study below). The work done by the Cystic Fibrosis Trust (https://www.cysticfibrosis.org.uk/the-work-we-do/clinical-trials-accelerator-platform) in terms of patient and clinical engagement, data accumulation and licensing, and partnership with industry to develop, trial and drive uptake of innovative therapies also inspires the design of CTANs, as do other instances of excellence found across the UK.

Critically, such initiatives have the capacity to build on the global contract research organisation sector by creating a 'one-stop shop', allowing accelerated delivery of industry sponsored trials within the UK through an autonomous commercially nimble trials delivery vehicle. Building on the success of such initiatives elsewhere across the world would make the UK a magnet for inward investment by the global biopharmaceutical sector, to the benefit of patients and UK PLCs.

Case study: Accelerating Clinical Trials – a new blood cancer trial delivery vehicle

Blood cancers remain one of the most common malignancies and there is justified excitement that the recent development by the global biopharmaceutical sector of a wave of potentially transformative new drug and cellular therapies could transform clinical outcomes. To take advantage of this opportunity, Accelerating Clinical Trials (ACT) Ltd (a company limited by guarantee) was established in December 2021 to accelerate the delivery of high-quality trials for blood cancers by addressing barriers to trial delivery, including: insufficient trial capacity to match the sudden expansion in the number of potential new therapies; outdated delivery models; and challenges to patient recruitment including the need to utilise genomic stratification.

Funded by a £5 million pump-priming grant from the charities Cure Leukaemia and Anthony Nolan and NHS Blood and Transplant, the ACT operational hub provides new trial delivery capacity for a mixed portfolio of clinically prioritised industry sponsored and academic investigator trials. In its first 12 months, ACT attracted investment from 2 international pharmaceutical companies to deliver 2 globally significant practice-informing trials in acute myeloid leukaemia and myeloma. ACT also provides secure funding for 2 transformative national trials acceleration networks which have recruited more than 2,500 patients to blood cancer trials in recent years: the Trials Acceleration Programme (TAP) for new drug therapies, and IMPACT, one of only 2 transplant trial networks in the world.

Central to ACT's mission is an 'umbilical' relationship with the DIDACT Foundation, whose membership includes senior clinicians, representatives of

the NCRI, philanthropists and patient representatives. ACT ensures clinical prioritisation of all its trials, provides funds for the training of research nurses and the next generation of clinical triallists, and will advise on reinvestment of future financial surpluses into new clinical trials. ACT's ability to deliver regulatory standard data allows it to accelerate delivery of a mixed portfolio of industry-sponsored and investigator-initiated trials through its networks, to the benefit of patients and the UK life sciences sector.

Case study: Protas

Protas (https://protas.co.uk/) is a UK-based not-for-profit organisation founded in 2021 to remove the barriers in the development of better treatments for common diseases and deliver trials that improve the health of those most in need. Large-scale, randomised clinical trials, which are vital to tackling the health conditions that have the biggest impact for billions of people worldwide, have become prohibitively costly and excessively complex. Protas seeks to drastically lower the cost of these trials while improving the quality of results, in order to increase the number of novel products being taken forward and opportunities to improve the health of populations around the world.

Working collaboratively with partners in pharma, philanthropy and academia, Protas designs and delivers large, late-stage, randomised clinical trials in a way that prioritises efficiency and quality over complexity. For instance, it only includes what is necessary to deliver a safe and effective result that answers the important question; it takes account of the perspectives of patients and medical staff to optimise the practicalities; and it uses technology to drive the efficiency and quality with which the trial is conducted. Protas engages regulators, payers, patients and clinicians, ensuring that each trial achieves the best possible outcomes for those set to benefit from it. This is underpinned by Protas' unique, scalable IT platform that can be configured to manage every aspect of multiple, concurrent trials from start to finish.

Protas is led by its Chief Executive, Professor Sir Martin Landray, who co-led the RECOVERY trial of treatments for COVID-19. Its team of globally recognised experts has decades of experience in conducting landmark clinical trials of novel treatments for common diseases, changing regulatory licensing around the world. Backed by a highly respected board, Protas is leading a new approach to clinical trials, one that realigns economic benefits with improvements in public health.

The NIHR CRN has published a primary care strategy (https://www.nihr.ac.uk/documents/nihr-clinical-research-network-primary-care-strategy/29999) which sets out the problems in research in primary care, including a reduction in patient recruitment numbers in studies managed by primary care sites, and a significant drop in the number of participating practices. The strategy outlines some of the blockers to increasing research activity such as a lack of academic opportunities for GPs and other healthcare

professionals in the setting, a rapidly changing landscape of primary care provision, increasing workload, transfer of work from secondary care, inadequate research funding, and the need for a cultural shift across the sector towards acceptance of this setting as fundamental to wider research delivery and best patient care.

Clinical trial acceleration networks (CTANs)

Recommendation 26: a new 'enhanced service' option should be developed, through the proposed CTANs, to enable the government and the NHS to develop an excellent process for every step of a trial. This will further research in the selected fields and create an exemplar for improving the service for all trials in the future

NIHR and its partner bodies across the UK should begin by commissioning 8 to 10 CTANs during 2023 through an open competition, to which consortia can apply. Each consortium would need to demonstrate that it would:

- provide joint leadership between industry, NHS, academic and the medical research charities
- focus on a field that has high unmet need, a large addressable market, or is otherwise globally significant in its potential
- align to the strategic interests of the UK
- would be capable of delivering a significant and growing level of clinical trial activity over time

There are different ways in which the government could choose areas of focus. Aligning with life science missions is logical. For example, the leadership of the Dementia Mission is now in place and there is a flow of new drugs coming through the pipeline from multiple companies. Creating a CTAN for Alzheimer's disease would, alongside the Dementia Translational Research Collaborative, enable the UK to have the world's best platform for clinical trials in this field.

Alternatively, the UK could also focus on areas of existing strength, such as cell and gene therapies, or take a more agnostic view, as ARIA has done with its recent call for programme directors, where proposals are invited and judged against a set of general criteria. This could include reducing health disparities, accessing new therapeutic modalities, or for trials in the new field of digital therapeutics.

Ideally, CTANs should align with priorities that can justifiably utilise the 'urgent public health' criterion that was exercised as part of the pandemic response prioritisation, including for NIHR (https://www.nihr.ac.uk/about-us/our-key-priorities/covid-19/) and the HRA (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/public-health-emergency-research/), to provide legitimate reasons for access to enhanced services in critical areas, such as regulation, information governance and clinical prioritisation.

Essential features of an enhanced service

CTANs will be tasked and resourced with delivering excellence in every part of running a trial, from planning and preparation, fast and streamlined approval and set-up processes and innovative approaches to conducting trials - including use of digital tools, access to data and ongoing communication between sites, co-ordinators and sponsors. The minimum requirement of the service, therefore, will be that the metrics set out for the significant recommendations above will be met for every step of the process.

Further enhancements should include:

- significant time commitment from a set of national clinical research leaders with expertise and capability to deliver in the field
- a network of trial-ready sites and a pipeline of potential future sites. Additional financial incentives to be provided to PIs and CIs to build additional research networks
- genuinely world-leading performance against the KPIs set out above, aiming to match those delivered by leading countries in this field. This would, for example, mean an even more rapid MHRA approval process than the agency set out to deliver in its Clinical Trials Regulation consultation response
- specific infrastructure requirements, such as access to radiology and pathology services, pharmacists and clinical research nurses
- overcoming barriers to accessing patient records appropriately to optimise research opportunities for patients by, for example, using the ‘substantial public interest’ clause of General Data Protection Regulation (GDPR) to provide a legal basis for this activity. Subject to rigorous patient and public engagement, specific regulatory notices could be enacted on specific disease areas within a CTAN to enable data flows, as was successfully implemented to enable the PRINCIPLE trial during COVID-19, which was still required to comply with GDPR (case study above)
- targeted campaigns to generate public interest in research in concert with relevant medical charities
- privileged treatment by regulators and access to ILAP to expedite the path to marketing authorisation and reimbursement

Criteria for successful delivery model

To ensure that each CTAN is delivered to meet the needs of the NHS and commercial partners, and to use private investment most effectively to drive improvements in patient care and economic growth, the service should be co-funded by the government, the NHS, industry and medical research charities. As an enhanced service that builds on our existing capacity, CTANs will require a small amount of additional public investment so that they deliver additional activity, rather than a prioritisation exercise to move resources from one area to another.

However, the government should not develop the CTANs on a ’build it and they will come’ basis. Unless public funding can attract significant external investment, from industry, philanthropy and academia of medical research charities, then that CTAN should not go ahead. Implementation of CTANs will, therefore, require very close working with industry to develop a model that effectively uses private sector funding for the benefit of patients and provides a commercially attractive proposition to companies.

Experience of previous ‘concierge’ type services has demonstrated that delivery fails where the leader of the service is either in one of the organisations involved in the process, and therefore, lacking in oversight and visibility of the other organisations, or where the leadership is new to the system and therefore cannot add value to the work of existing delivery partners and instead provides an additional layer of bureaucracy rather than streamlining.

To avoid these pitfalls, an ideal service would combine the existing expertise in all delivery partners across the system, with named accountable leaders in each organisation and appropriate resource to support additional workload, but also a clear leadership with sight of different parts of the process to effectively join up delivery, and give industry and charity partners a very clear ‘access point’. At both levels, it will be crucial to have robust accountability for performance, and clear metrics.

Delivery partners could be drawn from any part of the health and life sciences ecosystem, including public, private and academic sectors. Independent sector hospitals and healthcare providers should also be able to participate in this programme. The partnerships that Boots and Pharmacy2U have with the Our Future Health programme, for example, provide excellent examples of how private sector expertise can be used to deliver additional capacity in large population trials without creating additional burden on the NHS. The NHS-Galleri study similarly used mobile units to reach a wide and diverse group of trial participants, recruiting 140,000 to the trial in just 12 months (see case study above).

Part 4: implementing these recommendations

Recommendation 27: an action plan should be developed, to report by autumn 2023, outlining how the government and delivery partners will implement the recommendations of this review. The Life Sciences Council should provide objective accountability for the delivery of this action plan by the government and its agencies

While some of the actions recommended by this report will require longer-term work to implement fully, it is crucial that work is started immediately so that clear and visible progress is made across all recommendations to recapture industry confidence.

No significant policy and behavioural change ever happened because someone published a report, and this is no exception. The transformation we all seek to deliver in commercial trial activity will only happen with robust and rapid implementation. To that end, this report tries wherever possible to be specific in the actions required, to set deadlines, to push for clear KPIs and transparency on performance data, and to be clear which organisations are responsible for delivery.

In addition, and because of the broad range of changes needed across multiple bodies and the 4 countries of the UK, an additional accountability mechanism is required. To that end, a new working group should be created under the aegis of Life Sciences Council – co-chaired by ministers from both DHSC and DSIT, with the secretariat provided by the OLS and staffed with senior officials from the NHS, relevant departments and the devolved governments, to develop and oversee the implementation of an action plan based on my recommendations and to report on it publicly every year.

Despite best endeavours, there are no doubt areas where my recommendations could be further improved, so as it goes about considering its response to the review, I would urge the government to continue engaging with the clinical research sector to make them even more transformational.

Annex A: defining terms and scope

Clinical trials

Clinical trials are a form of research in health, to compare the effectiveness of 2 different treatments to each other. This comparison is done by treating a group of patients with the product being tested, and comparing that to the ‘standard of care’ (in other words, the treatment that a patient would usually receive in the NHS). Conducting clinical trials in the NHS is a crucial part of continuing to provide the best care to patients – ensuring that NHS patients receive the most innovative, cutting-edge treatments and are cared for by clinicians whose professional training and development is enriched by research.

All products being tested in clinical trials will go through a series of ‘phases’ of trial to test effectiveness. At phase 1, a product is being tested in humans for the first time and a small number of people are involved to understand possible side effects. At phase 2, a larger number of patients receive the treatment, and in many cases, this will be compared to a control group, for example, receiving a placebo, and the efficacy is measured.

Once a product has passed phases 1 and 2, it will go on to phase 3 where a larger patient population is tested and compared to a ‘control group’ that receives the ‘standard of care’ treatment provided by the NHS. This is to understand the effectiveness of the new product compared to the existing treatment options, and whether it will be beneficial for patients.

Once a product has passed phase 3, it may receive regulatory approval for use, and could be provided to NHS patients. Some products may also enter phase 4 trials, after regulatory approval has been granted. This is to gather further evidence about the effectiveness of its use in practice. More detail on different types of clinical trials can be found at the NIHR Clinical Trials Guide (https://www.nihr.ac.uk/documents/clinical-trials-guide/20595).

This review is focussed on mid- to late-phase trials, mainly phases 2 and 3, because most of the feedback received from representatives of the life sciences industry suggests that this is the part of the pipeline in which the UK's performance is seeing the most decline. As a lot of the requirements for running trials are similar for all phases, some of the recommendations will be relevant for phases 1 and 4 trials as well.

The review is specifically considering the environment for commercial trials, which are considered to be: those funded (in whole or part) by a non-government organisation; conducted by or on behalf of industry, including life sciences companies, often with the involvement of medical research charities); and those that use treatments or diagnostics, for example, medical technologies, biologics, vaccines, or medicines, provided without charge to the NHS for use in the trial.

System leaders

The National Institute of Health and Care Research (NIHR)

The NIHR is the largest funder of clinical research in the country and is centred on England, but collaborates closely with the devolved governments in Scotland, Wales and Northern Ireland. NIHR is funded by DHSC and it funds and supports research in the NHS and wider health and care system.

Commercial sponsors of trials are eligible to request their trials receive support from the NIHR CRN and be included in their portfolio. NIHR CRN portfolio studies benefit from access to support and services provided by the NIHR CRN, which works with sites to deliver studies to time and target, through:

- planning studies: including providing expertise in planning, costing and delivery within the NHS, as well as ensuring any research is inclusive
- site identification: NIHR CRN can help identify sites interested in participating and the feasibility of delivery
- performing and delivering the studies: the NIHR CRN can assist sites in streamlining set-up and ensuring the study remains on track to deliver, and provide services such as good clinical practice (GCP) (https://www.nihr.ac.uk/health-and-care-professionals/learning-and-support/good-clinical-practice.htm) training to ensure sites have the necessary skills and knowledge to deliver trials

Public investment in trial infrastructure is a major factor for commercial sponsors when choosing where to do their research. High-quality support and investment in trial infrastructure from public organisations ensure companies can deliver cost-

effective and efficient trials. Companies might also choose to use a clinical research organisation, which can support commercial sponsors of trials to oversee and delivery on clinical trials on the company behalf.

NIHR invested £23.2 million in the Clinical Research Facilities (CRF) in 2020 to 2021 to support the delivery of early-phase trials. Research networks such as the ECMC network further enhance early-phase performance by enabling sites to share best-practices and co-ordinate trial delivery.

The NIHR CRN portfolio captures around 85% of trials approved by the MHRA (https://www.nihr.ac.uk/documents/impact-and-value-of-the-nihr-clinical-research-network-2019-infographic-summarising-key-findings/22486). In 2021 to 2022, there were nearly 6,400 studies in the NIHR CRN portfolio, with around 1,700, or 26%, of these having a commercial sponsor. The number of commercial trials in the portfolio has gradually increased from 1,100 in 2015 to 2016, with an exception in 2020 to 2021 due to the pause in research due to COVID-19 (https://www.nihr.ac.uk/about-us/who-we-are/our-research-performance/annual-statistics.htm).

Five NIHR Patient Recruitment Centres (PRCs) were opened in 2020, as part of the government's Life Sciences Industrial Strategy and Life Sciences Sector Deal 2, with seed funding of just over £2 million in 2020 to 2021. Their purpose is to increase NHS capacity to deliver commercial research, make it easier and quicker to do this, provide opportunities for patients to benefit from early access to innovation, and provide a test bed for innovation in clinical trial delivery. However, their impact was inhibited through opening during the first COVID-19 pandemic lockdown, their limited number (compared to 54 CRFs and 18 ECMCs) and seed funding only for an initial 3-year period. They have been shown to have some success, with an average time of 43 days from site initiation to the first patient (https://local.nihr.ac.uk/news/new-figures-reveal-patient-recruitment-centre-successes/31208).

NHS Research Scotland

Clinical research activity is supported by NHS Research Scotland (NRS) (https://www.nhsresearchscotland.org.uk/) through partnership working between the Chief Scientist Office (CSO) of the Scottish Government and Scottish health boards. NRS supports the delivery of studies across a spectrum of disease and clinical need. Research within Scotland lies within the remit of at least one topic network or specialty group (SG), the key national bodies for supporting clinical research activity in Scotland, which act as an interface between the research community, the NHS and patients. NRS also works with Scottish universities and other organisations to ensure that Scotland provides the best environment to support clinical research.

Working closely with industry is a key priority for NRS. The NRS Industry Partnership Forum, formed in 2010, liaises between the CSO, NRS, the life sciences industry and patient representatives to increase clinical research in Scotland. The forum is co-chaired by CSO, ABPI and the Scottish Life Sciences Leadership Group.

Health and Care Research Wales

Health and Care Research Wales (https://healthandcareresearchwales.org/) supports the NHS in promoting and supporting health and care research. Health and Care Research Wales brings together partners across the NHS in Wales, local authorities, universities, research institutions, third sector and others to ensure research is of the highest international scientific quality and is relevant to the needs and challenges of Welsh health and care. In recognition of the link between improved care and high-quality research, Health and Care Research Wales encourages all health and social care professionals to get involved in research and offers resources and training to help health and care professionals contribute to the delivery of research.

Health and Care Research Wales invests in speciality leads to champion and support research development and delivery by building networks of PIs within their specialty in Wales and supporting the uptake of studies.

The Northern Ireland Health and Social Care Research and Development (HSC R&D) Division

In Northern Ireland, HSC research is supported through the HSC R&D Division of the Public Health Agency (PHA) (https://www.publichealth.hscni.net/directorates/public-health/hsc-research-and-development-wwwresearchhscninet). The HSC R&D Division is aligned to 5 strategic priorities in its current strategy of:

- developing an enabling infrastructure to support R&D
- building research capacity for R&D
- funding R&D
- supporting innovation as a means of transferring R&D findings into practice
- ensuring patient and public involvement in R&D

The HSC R&D division also sets out to deliver on its 10-year strategy, ‘Research for Better Health and Social Care’, which sets out how the health, wellbeing and prosperity of the Northern Ireland population will benefit from Northern Ireland-led health and social care research.

Regulators: the Health Research Authority (HRA) and the Medicines and Healthcare products Regulatory Agency (MHRA)

In the UK, the MHRA and the HRA provide approval for clinical trials. All trials must be approved by the HRA and RECs across the UK, and some require MHRA approval.

The MHRA is an agency of DHSC and is the UK regulator of medicines, medical devices and blood components for transfusion responsible for ensuring their safety, quality and effectiveness. The MHRA is responsible for Clinical Trials Authorisation (CTA).

The HRA was established in 2011 as an arm’s length body of DHSC with the ambition to transform UK research regulation and governance. The HRA and the

devolved governments provide a RES so that research proposals relating to their areas of responsibility can be reviewed by a REC. RECs protect the rights, safety, dignity and wellbeing of research participants. The HRA has published information on its approvals (https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/hra-approval/).

As of 2022, all trial applications that need approval from both the MHRA and RECs in the UK are subject to combined review, which means a single application goes to both bodies at the same time (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/combined-ways-working-pilot/). Before 2022, applications could be initially submitted to either body, with the timelines for approval being longer because they were completed sequentially not in parallel as in combined review, where a response or request for further information being provided in 30 days. The maximum time for combined review process is 60 days.

The Medical Research Council (MRC)

Under the umbrella of UKRI MRC works across the whole of the UK, investing over £600 million per year in research to tackle health challenges. MRC supports life sciences research including by (https://www.ukri.org/publications/mrc-strategic-delivery-plan/mrc-strategic-delivery-plan-2022-to-2025/): funding discovery science, and strengthening translation; fostering national and international partnerships; and supporting the breadth and diversity of skilled people needed for the future research and development workforce.

One specific initiative funded by MRC is the Clinical Trials Unit in partnership with University College London (UCL) (https://www.mrcctu.ucl.ac.uk/), which runs trials in cancer and infectious disease. MRC-funded research covers discovery, pre-clinical development, including animal studies, through to early clinical research, enabling the identification and initial assessment of new interventions, with early clinical to applied and implementation research being funded via the NIHR.

Another UKRI council, the Engineering and Physical Sciences Council (EPSRC) also makes important contributions here, including in the development of innovative imaging, diagnostic and digital health interventions. MRC and EPSRC discovery science thereby provides a pipeline of new potentially transformative ideas, technologies, such as monoclonal antibodies, cell and gene therapies, digital health, and methods that NIHR, often working in partnership with industry, can then pull through into benefit for patients and improved NHS services.

Health Data Research UK (HDR UK) is funded by MRC (lead), Economic and Social Research Council, EPSRC, NIHR, Health and Care Research Wales, HSC PHA Northern Ireland, CSO Scotland, the British Heart Foundation and Cancer Research UK. It delivers health data intensive research programmes and UK-wide data research infrastructure capabilities and services to enable the use of health-related data at scale for research and innovation. HDR UK also supported the development of NHS DigiTrials through the Digital Innovation Hubs programme.

Process for running a clinical trial

The process for establishing a clinical trial is multi-stage, so we have set out below the main components:

- planning a trial and identifying sites
- approval to run a trial
- costing and contracting
- recruitment of patients
- delivery of the trial
- dissemination of results

NIHR has published a toolkit (https://www.ct-toolkit.ac.uk/) which sets out the process of running a trial, and the below summarises the information it presents, and there is a specific industry route map published to help sponsors to navigate the NIHR system (https://industryroutemap.netlify.app/story_html5.html?lms=1).

Trial planning and site identification

Before planning a trial, researchers will: identify the research question; summarise the underpinning science to support the hypothesis; and consider the prioritisation of the research question. Once the preliminary work is completed, the trial will be designed including elements such as: the population – people to be included in the trial including recruitment criteria; intervention – defining what is being trialled; the comparator; and the outcomes, including data requirements and analysis plans. Before getting to the stage of making these plans within a country, or set of countries, global companies will seek evidence that their medicines will be delivered to patients and there is a successful market in the country to facilitate production and distribution, for example, by considering:

- access and uptake of new medicines: countries with high levels of patient access to new medicines and sequentially high uptake of those medicines will ensure medicines deemed safe and effective from a trial are likely to be utilised within the country of the research quickly
- how the wider UK life science industry is performing: countries with a thriving sector will ensure sequential R&D and innovation can take place following their research
- wider regulatory environment: to reduce the overall burden of regulatory approvals, companies will seek to run trials in where regulatory approval processes will support approval in other countries both for trials and market access
- alongside the overall design of a trial, sponsors must be agreed, and agreement must be reached on the funding of the trial, how data will be collected during the trial, and the risk assessment process. Trial sponsors must decide where trials can be delivered. In the UK, this is based on understanding the capacity and capability of sites to run trials

- sites are approached during planning of a trial, and undertake capacity and capability checks to determine whether they can take part in the running of the trial

Trial approvals

Once the trial has been planned, the sponsor must obtain approvals from regulatory bodies; principally, the MHRA and RECs, depending on the type of trial. The Integrated Research Application System (IRAS) is in place across the UK to provide a single system for trial sponsors to apply for approvals.

The approvals required for trials are:

- CTA from the MHRA
- research ethics approval from the HRA RES

As set out in the above section, a combined review is in place for both the MHRA CTA and REC approval to be handled under the same application where both are needed.

There is no requirement for site-level approval, but evidence gathered by this review and others demonstrates that requirements imposed by sites, alongside capacity and capability checks, create delays to progressing trials.

An approved protocol is required before a trial can commence.

Costing and contracting

To run trials in NHS sites, sponsors need to reach agreement on contractual terms of the trial delivery including costing. The NCVR was put in place to introduce a national streamlined approach to this service for commercial trials (https://www.england.nhs.uk/aac/what-we-do/embedding-research-in-the-nhs/national-contract-value-review/). It was first introduced in 2018 to 2019, and delayed by the COVID-19 pandemic, with implementation beginning in April 2022. Since October 2022, all commercial contract research studies being submitted for a study resource review have entered the NCVR process, and eligible studies will have a single costing using a standardised costing methodology. However, only around half of NHS trial sites have signed up to accept the local cost generated by this process without further negotiation. Alongside the NCVR, the UK has introduced the iCT to provide a standardised methodology for agreeing costings for trials.

Site set-up

Once the contract and costing have been determined for a trial, the sites must put in place resources to deliver it. The R&D leaders at a site carry out assessments to ensure that the site has the staff, time, equipment and expertise to carry out the trial safely. When the site leaders are confident that they have the resources and capacity in place to run the trial, they will sign the contract, including agreeing to costings. This process involves assurance of plans for pharmacy and radiology, as required by the trial protocol. More information about the pharmacy assurance

process is on the HRA website (https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/technical-assurances/pharmacy-assurance/applying-pharmacy-assurance/). This stage of process is inconsistent, as it depends on decisions made by individual NHS organisations and adds delays to the time for setting up a trial.

Recruitment of patients and delivery of trial

Informed consent:

Once all approvals are in place, contracting and costing completed, site capacity and capability checks are completed, and the trial site is set-up, the recruitment of patients can start. The vital first step to recruiting patients is identifying relevant patients and securing their informed consent to take part in the trial.

Ongoing monitoring during the trial:

During the trial, there is ongoing monitoring, to ensure the safety of participants as the sponsor is responsible for safety reporting, and the MHRA inspects sites, where relevant – for clinical trials of medicinal products, to ensure the trial is run according to GCP as set out by the Clinical Trials Regulations.

Communication and follow up with participants during and after the trial is critical. After the completion of the trial, researchers will disseminate results including following up with participants.

Annex B: terms of reference - clinical research advice

Background and purpose

The Life Sciences Vision Delivery Board, which is co-chaired by DSIT (formerly BEIS) and DHSC ministers, agreed that independent advice on the clinical research system was needed, in light of current issues in UK clinical research with commercial trial progress and productivity.

In March 2021, the government published its 10-year vision ‘Saving and Improving Lives: The Future of UK Clinical Research Delivery’, which was followed by an implementation plan for 2022 to 2025, published in June 2022. The UK RRG programme was initiated in December 2020 to bring together the delivery partners across the UK including in the NHS, the NIHR CRN, and industry, academic and charitable delivery partners to provide system leadership, oversight and strategic co-ordination of the work to implement the plans to deliver of the ambitions set out in the Life Sciences Vision for UK clinical research delivery. The UK RRG programme is co-ordinated by DHSC and is making progress across a number of commitments.

Work was undertaken in 2020, through a restart framework to support local decision-making, and in 2021, to take a managed recovery approach to co-ordinate

and sequence the delivery of a sub-set of multi-centre studies to clear the path for other studies, did not have the impact expected. In February 2022, it was considered that the research system would not recover without further intervention at scale, with the need to act quickly paramount.

A series of actions is being taken to recover the UK's capacity to deliver research through the Research Reset programme. DHSC is working in partnership with NHSE to ensure new studies are able to open and be delivered within planned timescales, while addressing the backlog. The Research Reset programme is having an impact and making progress across key indicators, but commercial trials are not recovering as quickly as non-commercial and significant issues still exist. Further work is now being undertaken to specifically target improving metrics for commercial clinical trials, including site set-up, contracting and recruitment. The overarching goal for the UK RRG programme is to deliver short-term actions and tackle other long-standing issues that require further system-wide reform.

A recent ABPI publication sets out a 44% drop in patients recruited to commercial clinical trials that were supported by the NIHR in the last 5 years. This was exacerbated by the effects of the COVID-19 pandemic in 2020 to 2021, during which the UK recruited over a million participants to COVID-19 research. However, prior to the pandemic the UK had already seen recruitment to commercial trials drop, with nearly 50,000 patients recruited in 2017 to 2018 compared to under 29,000 in 2019 to 2020 (https://www.abpi.org.uk/publications/rescuing-the-uk-industry-clinical-trials/). We need to act to reverse this trend to re-enable the clinical research system to maximise growth and productivity. The ABPI publication has set out a list of actions that it sees as supporting such recovery.

The clinical research vision has strong industry support, and there is agreement about the issues it highlights and plans to address these, with a need to see faster progress on implementation and a focus on key priorities.

This independent advice is being commissioned by ministers to ensure growth opportunities are maximised, and expedited progress is made to resolve the key challenges in conducting commercial clinical trials in the UK.

As part of the advice process, there will be a need to review pre-existing and ongoing work to improve UK clinical research, particularly in relation to commercial clinical trials, and to build on this with focussed engagement with expert stakeholders. The starting point for the review, will be that it should focus on commercial phases 3 and 4 studies, with a consideration of how the environment for earlier phase research impacts these. This is to be tested with stakeholders.

Objectives of the review

The advice will focus on commercial clinical trials in the UK, and be carried out with the following objectives:

- to recommend a shortlist of priority actions, to make progress in 2023. These actions need to:
  - prioritise within ongoing work

    - take into account impacts on other parts of the system and other sub-sectors
    - consider feasibility for delivering actions
    - have clearly assigned ownership (single or joint)
- alongside these recommended priority actions, the advice will take a view of the longer-term ambitions for UK clinical trials
- to utilise the wealth of existing evidence, and recommended actions, to provide a clear set of priorities, seeking to limit any additional burden on expert stakeholders who are already active in working to improve the system
- to report speedily, early in 2023, with a final report by end of Q1 2023

Governance of the review

The following governance arrangements have been agreed for the review:

- the advice chair has been appointed by DSIT (formerly BEIS) and DHSC ministers as an independent chair, who will make recommendations and engage with senior stakeholders
- the independent chair will meet with ministers before and during the process of producing the advice, to provide updates and share emerging findings
- all external-facing products produced as a result of this advice will be the responsibility of DSIT and DHSC

Ways of working

The following ways of working arrangements have been agreed for the review:

- the advice will be delivered at pace, over 8 to 10 weeks
- all information that will be shared by stakeholders as part of the review process is privileged and should not be shared more broadly without the consent of DSIT and DHSC
- the advice will be supported by a secretariat with the capacity and skill required to support the chair and engage with a wide range of external stakeholders
- the secretariat will provide the chair with comprehensive background information, covering all previous reviews and strategies in this field, as well as action plans and recommendations from industry
- this secretariat will be led by an independent chair as detailed above, who will lead the delivery of the objectives set out in the above section
- these terms of reference may be amended, varied or modified with the agreement of DSIT and DHSC and the consultation of attendees

Annex C: organisations engaged during the review process

- Abbott

- Academy of Medical Sciences
- Actaros Consultancy Limited
- Apex Ventures
- Association of British HealthTech Industries (ABHI)
- Association of Clinical Research Organizations (ACRO)
- Association of Medical Research Charities (AMRC)
- Association of the British Pharmaceutical Industry (ABPI)
- AstraZeneca
- Balanced CR
- Barts Health NHS Trust
- Barts Life Sciences
- Behold AI
- Birmingham Health Partners
- Blackpool Teaching Hospitals NHS Foundation Trust
- Blood Cancer UK
- Boehringer Ingelheim
- British Heart Foundation
- British In Vitro Diagnostic Association (BIVDA)
- Cancer Research UK
- Catalent
- Clerkenwell Health
- Clinical and Contract Research Organisation (CCRA)
- Clinical Innovation Partners
- Department of Health and Social Care (DHSC)
- Faculty of Pharmaceutical Medicine
- Federation of Specialist Hospitals
- Francis Crick Institute
- Gilead Sciences, Inc.
- GSK
- Health Data Research UK (HDR UK)
- Health Research Authority (HRA)
- Health Research Wales
- House of Lords Science and Technology Committee
- Huma
- Icon plc
- Imperial College Healthcare NHS Trust
- IQVIA
- Janssen
- Johnson & Johnson

- Labcorp
- Lakes Bioscience
- Lightship
- Lilly
- Lindus Health
- Lonza
- Medicines and Healthcare products Regulatory Agency (MHRA)
- Moderna
- MSD
- National Institute for Health and Care Excellence (NICE)
- National Institute for Health and Care Research (NIHR)
- NHS Digital
- NHS England (NHSE)
- NHS England Innovation, Research and Life sciences (NHSE IRLS)
- NHS Improvement
- NHS Providers
- NHS Research Scotland
- NIHR Clinical Research Network (NIHR CRN)
- NIHR Clinical Research Network Greater Manchester (NIHR CRN GM)
- NIHR Clinical Research Network North West London (NIHR CRN North West London)
- NIHR Clinical Research Network West Midlands (NIHR CRN WM)
- NIHR Leicester Biomedical Research Centre (NIHR Leicester BRC)
- NIHR Patient Recruitment Centre Programme Office
- NIHR Patient Recruitment Centre: Leicester (NIHR PRC: Leicester)
- NIHR Patient Recruitment Centre: Newcastle (NIHR PRC: Newcastle)
- Northern Ireland Executive
- North West E-Health
- Novartis
- Novo Nordisk
- Nye Health
- Office for Life Sciences (OLS)
- Office for Strategic Coordination of Health Research (OSCHR)
- Oxford University Hospitals NHS Trust
- Paradigm, Inc.
- Parexel
- Pfizer
- Pharmaron
- Phillips

- PPD, Inc.
- Public.io
- Queen Elizabeth Hospital Birmingham
- Queen’s University Belfast
- Quell Therapeutics
- Quotient Sciences
- Quibim
- Roche Diagnostics
- Royal College of Physicians (RCP)
- Scottish Government
- Seqirus
- Shelford Group
- Silence Therapeutics
- Stitch Health
- SV Health Investors
- Syneos Health
- ThermoFisher
- UK BioIndustry Association (BIA)
- UK Clinical Research Facility Network (UKCRF Network)
- UK Health Security Agency (UKHSA)
- University College London Hospitals NHS Foundation Trust (UCLH)
- University Hospital Southampton
- University of Birmingham
- University of Manchester
- University of Oxford
- Weatherden, Ltd
- Wellcome Trust
- Welsh Government

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