PANORAMIC
Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community

NIHR | National Institute for Health and Care Research

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES
UNIVERSITY OF OXFORD

NIHR Clinical Research Network

The PANORAMIC study of COVID-19 treatments in primary care: a review and learning exercise

Evans P, Tonner E, Williamson J D, Dolman M, Chambers E, Crawshaw S E and Yu L-M.

Study IRAS Number: 1004274

August 2024

NIHR | National Institute for Health and Care Research

Report Sections

Tables, Figures and Case Studies

Figures

Tables

Case Studies

1. Foreword

Ever since the start of the COVID-19 pandemic in early 2020, primary care and primary care research have been undergoing unprecedented and rapid change. The **Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community (PANORAMIC)**, the fastest recruiting and the largest trial of a therapeutic agent for COVID-19 ever in primary care, has just closed to recruitment. It is therefore opportune to review and reflect on the lessons learned from the delivery of this major UK-wide trial that is informing care and guidelines in the NHS and world-wide.

The many contributors from different professional backgrounds and the wide range of topics highlighted in this report illustrate the collaborative nature of research, which was demonstrated powerfully during the pandemic. Despite adverse conditions in the public, professional and private lives of health and research professionals, colleagues stood up to deliver urgent public health studies, and PANORAMIC, against the odds, and in many cases they went 'above and beyond'.

This report is therefore a collection of contributions from all concerned in the design and delivery of the trial. However, it is primarily written from the **perspective of research delivery** through the National Institute of Health and Care Research Clinical Research Network (NIHR CRN) in England and the analogous networks in Wales, Scotland and Northern Ireland. It includes reflections about the delivery of the study across the four UK nations, talking in detail to those involved, and is therefore probably the first of its kind. It includes considerations of both the successes but also the challenges of conducting a study such as this in the pandemic environment. It inevitably touches on aspects of research design, but is predominantly about research delivery.

It is hoped that readers of this report, both now and in the future, will be able to reflect on our collective experience of primary care research in the COVID-19 pandemic and that this report will have a positive influence on the design and delivery of future studies. The main thrust of this report is to inform future studies conducted in primary care, both within and without a pandemic, but the broad principles derived from the delivery of this trial will apply to other studies in primary care, secondary care and across the health and social care research ecosystem.

I'm grateful to the NIHR CRN team and to the study team for constructing this report over the last year and strongly commend it to you.

Professor Philip Evans, Deputy Medical Director NIHR CRN, and NIHR CRN Clinical Link for PANORAMIC

2. Executive Summary

The 'Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community' or **PANORAMIC** study, led by Professor Chris Butler and colleagues at the University of Oxford, was one of the flagship primary care trials in the COVID-19 pandemic. Its sister trial, PRINCIPLE, tested the clinical effectiveness of repurposed drugs in patients with mild to moderate COVID-19 in the community. PANORAMIC was then set up to evaluate the clinical and cost-effectiveness of novel oral antivirals, i.e. molnupiravir (Lagevrio) and nirmatrelvir-ritonavir (Paxlovid) in a platform trial delivered in primary care.

The trial was delivered in collaboration with the NIHR Clinical Research Network (CRN) in England and partner networks across Northern Ireland, Scotland and Wales. The NIHR funds, enables and delivers health and social care research that improves people's health and wellbeing and promotes economic growth. The NIHR Clinical Research Network (CRN) is a national research network in England that coordinates and supports the delivery of high-quality clinical research across health and social care.

PANORAMIC is to our knowledge the largest randomised trial of COVID-19 therapeutics in primary care in the world. At the height of recruitment in early 2022, it was also the fastest-ever recruiting primary care Clinical Trial of an Investigational Medicinal Product (CTIMP) delivered through the NIHR CRN.

PANORAMIC recruited just under 30,000 participants into a randomised platform trial using innovative methods of recruitment that had not previously been tested in a primary care setting. This was made possible by the four nation UK-wide approach to the delivery of the trial and digitally supported delivery and outcome assessment.

Given the unique and historic nature of the trial, and the many innovations that were rapidly implemented, some more successful than others, it is essential that we reflect and learn from its remarkable achievements. The NIHR CRN team led this learning work along with members of the study team, and convened a series of meetings specifically asking key stakeholders for their reflections and learnings. These covered many diverse aspects of the delivery of such a complex trial drawing out important innovations but also key challenges. This report also forms an output of the NIHR CRN Primary Care Research Programme.

The details of the delivery of this trial are well documented in this report, both for clarification of precise delivery methods but also as an historical record of what is potentially an undertaking of global significance. There has been international interest in the delivery of this trial from other countries, some of whom were unable to adequately deliver COVID-19 research in a primary care setting. This report, therefore, will be of interest both to international academics but also to commercial trial sponsors beyond the UK.

Appreciating the length of the main document (available as a PDF to download), readers with specific interests may be interested in the following sections which contain detailed descriptions of the delivery of the trial relative to the following themes. If further information is required then the relevant appendices contain detailed descriptions for your information:

Pandemic preparedness and primary care	Section 8	Appendix 2
Primary care delivery models	Section 10	Appendix 3
Decentralised trials and remote trial delivery	Section 10, 13	
Research inclusion	Section 12	Appendix 7
Platform trials	Section 9	
UK-wide delivery of the trial	Section 15	

The trial itself has significant implications for the future delivery of both pandemic and non-pandemic primary care studies, and this report outlines the collective learnings from key stakeholders across all four nations. This report also includes wide-ranging recommendations to further enhance the delivery of primary care research trials, both in a pandemic but also in a non-pandemic situation and has demonstrated the potential impact of this large decentralised and remotely delivered trial to clinical research in the UK and beyond.

3. Recommendations

Based on the findings from this stakeholder engagement, we recommend the following:

Pandemic Primary Care Studies

1. In future pandemic research, due consideration should be given to the potential reach and impact of primary care studies from the very start of any pandemic, in order to ameliorate patients' symptoms and reduce hospital admission.
2. Primary care research infrastructure, such as existing Hub and Spoke models, should be in place to deliver platform studies of potential therapeutic agents.
3. Diagnostic platform trials could be integrated with therapeutic platform trials in primary care, and embedded in symptomatic and asymptomatic pandemic mass testing national programmes for maximal efficiency.
4. The concept of the delivery of a therapeutic agent within a randomised trial as part of clinical care, should be encouraged for future pandemics and more widely.
5. Close engagement with the respective taskforces, Government, regulators, funders, and the NHS was beneficial to the set-up and delivery of primary care studies within the pandemic and should be encouraged. Engagement should include the involvement of all four nations.

Design of Studies

6. Having a variety of delivery models, and the ability to flex in response to pressures in the system is vital. The study and site research teams should also participate in operational discussions from the start.
7. Work should be undertaken to further define how recruitment could be enhanced in care homes in any future pandemics.
8. Pragmatic primary care trials should seek to include both cost-effectiveness and mechanistic sub-studies using microbiological and immunological samples which can often be collected remotely. The impact of treatment on resistance and effectiveness of interventions in the face of emerging new strains could then be determined.
9. Engagement with funders, Sponsors, researchers and NHS England (NHSE) should be made at an early stage to review the extent of potential service support costs and excess treatment costs.
10. The use of clinical referrals as opposed to Participant Identification Centres (PIC) should be carefully considered, including the respective advantages and disadvantages.

Research Delivery

11. Centralised dispatch for studies (i.e. investigational medicinal products or testing kits) should be considered in study design. Ways of rapidly delivering medicine directly to participants at home should be further evaluated in trials, with lessons learned then applied to clinical deployment, should the effectiveness of interventions be proven.
12. NIHR Clinical Research Network (CRN) agile teams provide significant flexibility in delivery of studies and should be considered in future studies to facilitate efficient recruitment.

13. Involvement of Devolved Administration colleagues in early study design will ensure appropriate consideration of the language in regulatory documentation and data flows - which would prevent the need for subsequent amendments.

Platform Studies

14. A pragmatic approach is recommended for review of the SoECAT (Schedule of Events Cost Attribution Template) and site costings following any substantive change, either following amendments or when changing delivery methods.
15. Practices engaged in such primary care platform trials could also provide data for national syndromic surveillance and, with enhanced phenotyping, for sentinel surveillance.

Research Inclusion

16. A co-created equality, diversity and inclusion (EDI) engagement strategy should be developed to build trust and relationships and promote research inclusion.
17. There should be a broad-based, diverse mix of public and patient involvement and engagement (PPIE) activities, with an emphasis on EDI aspects beyond ethnicity and deprivation (such as those living with a disability).
18. The use of UK-wide pharmacy networks, including community pharmacies, to promote research inclusion should be considered for future similar trials in primary care to increase recruitment in underserved communities.
19. A hybrid design of central recruitment plus Hub and Spoke recruitment should be considered an efficient way of increasing the opportunity for people to engage in research, regardless of where they live or receive their healthcare.
20. In addition to translations, study teams should consider different communication channels, making messaging more effective and accessible.

Workforce

21. Research delivery staff should be trained in and, if possible, exposed to remote working as standard, to ensure they are equipped to work remotely, have more agility and be at lower risk of becoming ill themselves during infectious diseases outbreaks.
22. Standardisation of skills, experience and contracts moving forward would support agile and efficient working that can respond to the needs of the health and care system.
23. Clear governance arrangements and contracting guidance would better support collaborative working across NHS organisational boundaries, and across universities.

Digital Support and Engagement

24. Future studies of pandemic infectious diseases in primary care would benefit from an option for patients to register their positive tests within a national system. This would assist GP identification, as well as facilitating 'direct to patient' text messaging highlighting research opportunities.
25. Data should flow in a way that mirrors the patient journey through the system, and support recruitment at all stages of the trial process.
26. Established and streamlined processes will be needed to enable efficient retrieval of outcome data in trials of this scope and scale across the four nations.

27. The use of the Summary Care Record by the study team is recommended for similar decentralised trials in order to screen and check eligibility of potential participants across the four nations, without the need for the full GP record.
28. The NIHR CRN Primary Care Research Informatics and Digital Environment Solutions (PRIDES) system, using the clinical systems of GP practices to identify positive individuals, was well-received by GPs and should underpin the future delivery of this type of trial.
29. The use of the NIHR Systematised Nomenclature of Medicine (SNOMED) research codes recording invitation and participation in the trial was implemented successfully, and should be replicated for future primary care trials involving GP practices.
30. Although uptake of the NHS Digital Population Health Platform WebViewer was minimal at sites, it did demonstrate proof of principle in that data from NHS Digital could be used as an alternative method of identification of eligible individuals.

4. Methodology

As the pandemic progressed it became clear that the delivery of the PANORAMIC study broke new ground in so many different areas that it was important to take stock and review the collective learnings from the study.

In order to do this, a wide-ranging stakeholder workshop was held online on 2 February 2023, involving colleagues from the study team (including the CIs), the NIHR CRN Coordinating Centre, the local Clinical Research Networks (LCRNs), NHS England, NHS Digital (as was), regulatory colleagues from the Health Research Authority (HRA), and Devolved Administration research delivery colleagues (see full list of attendees below). A series of facilitated themed discussions were undertaken and, using a Google-specific tool (Jamboard), stakeholders were enabled to record their comments directly. After the workshop, these individual comments were further analysed and refined into specific themes which are addressed individually section-by-section in this report. One further deep-dive was undertaken in the digital domain using a similar methodology, building on the previous digital feedback.

5. Authorship

Writing Team

Professor Philip Evans: Deputy Medical Director, NIHR CRN Coordinating Centre (corresponding author).
Dr Emma Tonner: National Medical Director's Clinical Fellow, NIHR CRN Coordinating Centre.
Dr James D. Williamson: Research Delivery Lead, NIHR CRN Coordinating Centre.
Dr Mark Dolman: Deputy Chief Operating Officer, CRN Thames Valley and South Midlands (Lead Network).
Dr Emma Chambers: Research Delivery Lead, NIHR CRN Coordinating Centre.
Dr Sarah E. Crawshaw: Head of Research Delivery, NIHR CRN Coordinating Centre.
Professor Ly-Mee Yu: Co-Director of the Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences, University of Oxford.

Many individuals and stakeholders have contributed to the collation of this report. Details of all colleagues involved (and their affiliations) can be found in Appendix 1.

6. Disclaimers

The PANORAMIC study was funded by the NIHR (Award ID: NIHR135366). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

7. Acknowledgements

The writing group of this report gratefully acknowledges the widespread and productive engagement with all stakeholders, and their contribution to this report. We are also grateful to the individual sites across all four nations, and their constituent teams, who delivered the study, and to the study team for their leadership of the trial. Special thanks go to the Chief Investigators (CIs) of the study Professors Chris Butler, Paul Little and Richard Hobbs for their input into this report, and to Julie Allen and Lucy Cureton as PANORAMIC Senior Trial Managers, for their leadership and engagement with this process. We are also grateful to the thousands of participants who took part in this study, without whom the success of the study could not have been realised.

8. Introduction

8.1. Background to the Trial

At the onset of the COVID-19 pandemic in 2020, caused by the SARS-CoV-2 virus, the Department of Health and Social Care (DHSC) instituted the Urgent Public Health (UPH) Group in response to the urgent need for research in a pandemic setting. The UPH Group was convened by the National Institute for Health and Care Research (NIHR) Clinical Research Network (CRN), was chaired by the NIHR CRN Medical Director, and aimed to prioritise COVID-19 research studies to be delivered through the NIHR CRN.

As part of the initial COVID-19 pandemic response, it was recognised that there was a need for primary care research in less severely ill patients in the community, and to evaluate both diagnostics and therapeutics in a community setting. In view of this, the RAPTOR study (PI Richard Hobbs) was designed to test new diagnostics in this setting, and opened to recruitment in October 2020. To test therapeutics in a primary care setting the PRINCIPLE study was set up and opened to recruitment in April 2020, led by CIs Professors Chris Butler and Richard Hobbs with colleagues from the Primary Care Clinical Trials Unit (CTU), Nuffield Department of Primary Care Health Sciences, University of Oxford.

PRINCIPLE studied repurposed medications for COVID-19 in patients who had mild to moderate COVID-19 in the community and who had not been admitted to hospital and became one of seven publicly-funded, national priority platform trials, alongside RECOVERY, REMAP-CAP, AGILE, PROTECT-V, STIMULATE-ICP and HEAL-COVID. PRINCIPLE was designed as an adaptive platform trial (Hayward, et al., 2021) using Bayesian techniques, and subsequently went on to assess the clinical effectiveness of seven repurposed medications in primary care. These included hydroxychloroquine, colchicine (Dorward, et al., 2022), azithromycin (PRINCIPLE Trial Collaborative Group, 2021), inhaled budesonide (Yu, et al., 2021), doxycycline (Butler, et al., 2021), favipiravir and ivermectin (Hayward et al, 2024), all delivered through a master protocol with investigational medicinal product (IMP)-specific appendices. The only finding of a beneficial effect was that of inhaled budesonide on time to recovery, but not hospitalisation or death - the latter being the primary outcome for all arms.

In spring 2021, it became clear that there were a number of candidate novel antiviral drugs that had been rapidly developed, had some early evidence of benefit, and merited further evaluation in a large Phase III randomised trial. DHSC therefore commissioned the NIHR to advertise a call for a novel antiviral platform in primary care.

This was awarded in open competition in August 2021 to the same team from Oxford, in collaboration with other universities (including University College London, and the Universities of Southampton, Glasgow, Cardiff and Liverpool). It was expected that this antiviral platform would test both the clinical and cost-effectiveness of up to 3 novel antivirals already licensed by the MHRA with conditional marketing authorisations (CMAs). There was provision for a virology sub-study to assess virological endpoints, and also a post-exposure prophylaxis study (which did not take place due to the complexities of delivery), using each of the candidate drugs. It was specified at the onset of the platform that the primary outcome was to be the 'hard' outcome of COVID-19 hospitalisation and/or death.

The result was the 'Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community' (PANORAMIC) study (CIs Chris Butler, Paul Little and Richard Hobbs). This was an NIHR-funded and Antivirals and Therapeutics Taskforce (ATTF)-supported national priority study endorsed by the CMOs of all four UK nations, which sought to provide the evidence-base for decisions on the deployment of oral antivirals in primary care, including clinical and cost-effectiveness. Candidate drugs were assessed by the UK COVID-19 Therapeutics Advisory Panel (UK-CTAP) for the eight national priority, publicly funded trials and recommended for inclusion if appropriate. The first drug included in the PANORAMIC platform was molnupiravir (Lagevrio) developed by MSD, followed by nirmatrelvir/ritonavir (Paxlovid) developed by Pfizer.

8.1.1. PICO

As outlined in detail in the protocol paper (Gbinigie, et al., 2023) the initial PICO for PANORAMIC was as follows:

Population	• Positive polymerase chain reaction (PCR) or lateral flow device (LFD) test for Covid-19. • Clinically Vulnerable over 18 years • Anyone aged 50 and over • Symptoms max 5 days
Intervention	• Oral antivirals with initial efficacy and safety data from phase 2/smaller phase 3 trials • Molnupiravir intended as the first intervention • Then Paxlovid
Comparator	• Standard of care/usual care
Outcome	• Hospitalisation and death, and secondary outcomes including recovery, costs, safety, viral load, variants and resistance (sub-study)

Table 1. The PICO (Population, Intervention, Comparator, and Outcome) of PANORAMIC.

8.2. Progress of the Trial

After initial delays in the procurement and delivery of molnupiravir, the first participant was recruited into PANORAMIC on 8 December 2021, just as the Omicron wave commenced (see Figure 1). By 27 April 2022, 26,411 participants had been recruited into the molnupiravir and usual care arm, and in December 2022 the final clinical effectiveness results of the molnupiravir analysis were published in *The Lancet* (Butler, et al., 2023) after an initial pre-publication of preliminary results in October 2022.

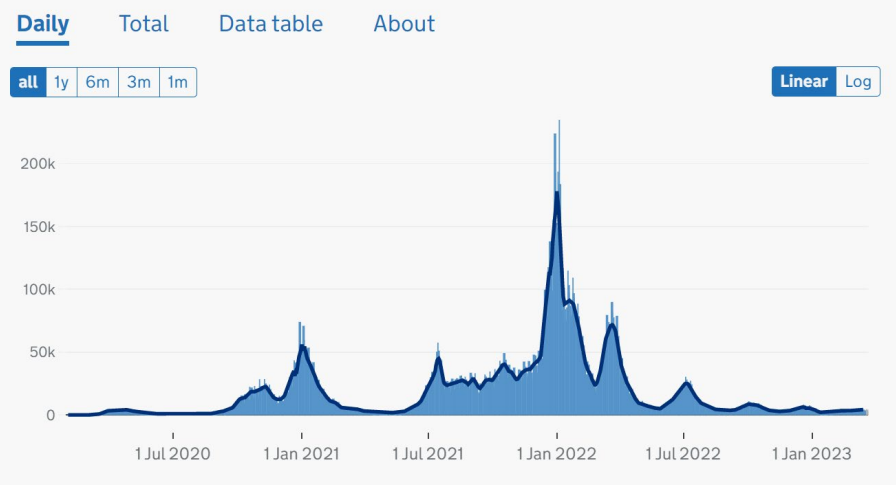

Figure 1. The trajectory of England COVID-19 cases during the pandemic. (Data taken from Cases in the UK | Coronavirus in the UK; this dashboard was decommissioned on 14 December 2023 and replaced by the UKHSA data dashboard)

The PANORAMIC trial continued to recruit into Paxlovid and usual care arms until the end of March 2024 (the study closed to recruitment on 28 March 2024). The final recruitment to the study as of 28 March 2024 was 29,293 participants, with the required sample size achieved for both the molnupiravir and Paxlovid arms of the study.

8.3. PANORAMIC Virology sub-Study

The virology sub-study in PANORAMIC collected samples from a subset of participants for viral and immunological analysis. Nasopharyngeal swabs and dried blood spots were taken by participants at home and sent to the central laboratory. Embedding a mechanistic sub-study into pragmatic primary care trials enables researchers to (a) better understand the study population, (b) discover the biological reasons behind the main study results, and (c) identify any unintended consequences of treatment. These insights can be key for policy makers in deciding whether to implement a therapy, especially where clinical results are finely balanced.

This sub-study showed that important biological observations can be made within a remotely managed primary care study without the need for participants to attend research sites or for clinical staff to take samples.

Current technology enables a wide range of measurements to be made in self-collected samples (including blood). Successful delivery of such a study requires clear instructions to participants (e.g. written and video), a robust audit trail of sampling kits and sample processing, rapid delivery of kits to participants, and a responsive laboratory with highly trained staff. Potential challenges include verification of sample provenance, issues of sample labelling (done by participants themselves) and the delay or loss of samples via the postal service.

8.4. Publications

At the time of writing this report there had been four publications relating to the design and findings of the trial. These included the molnupiravir clinical effectiveness paper (Butler, et al., 2023); the molnupiravir cost-effectiveness paper (Png, et al., 2024) and the molnupiravir

virology substudy (Standing, et al., 2024). The methodology of the trial was outlined in the protocol paper (Gbinigie, et al., 2023).

8.5. Operational Oversight

In October 2021 it became clear that PANORAMIC would be a nationally important study needing to be delivered at pace and scale across the UK, and the NIHR CRN stood up a small team (the NIHR CRN core team), led by Professor Philip Evans (Deputy Medical Director, NIHR CRN) as the clinical link for the study. This group included senior Research Delivery colleagues from the NIHR CRN Coordinating Centre and the lead Local Clinical Research Network (LCRN), Thames Valley and South Midlands, with other individuals invited as required (e.g. business analysts and workforce specialists), and met every working day for the two months prior to the first participant being recruited into the study. These meetings were reflective, proactive and reactive in nature, with no terms of reference, but were minuted and followed rolling agendas to ensure that points could be discussed as they arose.

Within this space, the group was able to review and oversee trial progress and NIHR CRN activity, and prepare for the wide range of other cross-stakeholder meetings which were convened to support the planning, set-up and delivery of the study. Further information about operational oversight activities, and meeting arrangements, can be found in Appendix 2.

8.6. The DHSC and Government Engagement with PANORAMIC

It was generally agreed that the UK Government / DHSC infrastructure, particularly CTAP, was of benefit to the trial and was missed once it had been stood down (September 2021). Through CTAP, expert recommendations regarding potential therapeutic agents were able to be shared directly with the CI and the study team, a model that would be considered important for future pandemic preparedness, while NIHR representation on the respective taskforces' strategy and programme boards enabled effective bilateral communication. It is notable that the Joint Advisory Access Mechanism (JAAM), a CTAP-like organisation, continued in Europe to assess new interventions coming into EU-funded trials.

Of particular importance was the central Government messaging around the prioritisation of COVID-19 research in the pandemic and the importance of a national research trial prioritisation process, aligned with a corresponding local prioritisation process, enabling the successful delivery of these platform trials at speed and scale in the NIHR CRN. This had not been experienced previously, but greatly enhanced the delivery of this specific study.

The role of the various Government COVID-19 taskforces and their support for the trial was valued. These included the ATTF, and its predecessors the Antivirals Taskforce (ATF) and Therapeutics Taskforce (TTF). At the launch of PANORAMIC trial, four high-level webinars were held, hosted by the Deputy CMO, Professor Jonathan Van-Tam, and the head of the ATTF, Eddie Gray, targeting dental, medical, nursing and allied health professionals and the third sector. The support given to the launch of the study was considered significant and had a huge impact across the sectors. It was acknowledged that these meetings would not have been possible without governmental and taskforce input. It was also noted that the institution of the governmental 'living with COVID-19' policy and the changes to the availability of free COVID-19 testing in April 2022 had a detrimental effect on the number of eligible participants,

though regular meetings with the study team and ATTF allowed the study to flex in response to these developments.

Inevitably, early in the pandemic, there was a concentration of national research on secondary care and intensive care treatments of COVID-19, and PRINCIPLE was the only primary care therapeutics platform. In future pandemics a reversal of this should be considered. If it is clinically appropriate, there should be an early emphasis on diagnosis and treatment in primary care, and hence preventing patients in the community being admitted to hospital.

Likewise, the national messaging and communications around the trial with linked public communications campaigns were considered essential, particularly with the launch of the digital texts to individuals with COVID-19 signposting them to the study website. This messaging was unique to the pandemic and should be considered, if appropriate, in future pandemics.

The parallel deployment of drugs with CMA authorisation to very high-risk groups through the COVID Medicines Delivery Units (CMDUs), alongside the provision of the drug in a randomised trial such as PANORAMIC for individuals at lesser degree of risk, was considered to be key learning from this study. This 'deployment in a trial' was unique to PANORAMIC. It did however create a degree of ambiguity, particularly for clinical colleagues, but it was an important distinction and highly relevant to the successful recruitment in spring 2022 when the Omicron variant was prevalent. It also necessitated close working between the NIHR and NHSE to ensure that there was a joined-up approach to this deployment in the trial or through the CMDUs. This was achieved through NIHR representation on NHSE deployment groups, as well as the four nation communications working group.

9. Platform Studies and Research Design in a Pandemic

Unlike conventional clinical trials that have a fixed number of interventions and trial duration, platform design is perpetual. This allows for the standard of care to change, and allows the trial to evaluate several candidate interventions at the same time (though interventions may not be introduced concurrently), to find out earlier how effective an intervention is, and to add or stop an intervention through emerging evidence while the trial is ongoing (Saville and Berry, 2016) .

When reviewing the set-up and delivery of PANORAMIC, the nature of the trial as a platform study and its impact on delivery was evaluated. It is noted that PANORAMIC acted as a platform study but only briefly, during an overlap between the two IMPs being investigated. Platform studies pose particular set-up and delivery challenges, such as the changing nature of the study (for example, due to the change of IMP being investigated), and requirement to revise on an ongoing basis.

On changing the IMP from molnupiravir to Paxlovid, a revision of cost attribution and costings was required to reflect the change in delivery of the IMP, for instance staff qualified to undertake informed consent and assessment of eligibility. There were no Excess Treatment Costs (ETCs) identified for PANORAMIC, but it is noted that if this had been the case this would have exacerbated the challenges of a change in IMP. Due to the short overlap between IMPs, a need for a funding model based on both drugs concurrently was also not considered.

However, on reflection, the principal challenges for the PANORAMIC study were not a result of the trial being a platform study but instead due to other factors, namely:

- **Scale of the study**: resulting in challenges in identifying the workforce required, the number of sites required, and magnifying any anomalies in funding requirements and payments.
- **Urgent nature of the study and speed of recruitment required**: resulting in pressure on workforce and resources. This required the need to continuously develop new recruitment strategies both on an ongoing basis and following amendment. This subsequently had follow-on implications for various funding flows and the nature of staff required. Additionally amendment changes pertaining to staff authorised to undertake activities would also result in changes in costings.
- **Study eligibility window**: a significant challenge was also that patients needed to be randomised and start treatment (if appropriate) within five days of onset of symptoms.

It is felt that if additional IMPs were utilised in this platform study or with further overlap, this would have exacerbated these challenges but not necessarily created novel challenges.

An advantage of conducting a platform design trial in primary care is that recruiting sites will only require to be familiarised with one single master protocol and the process of recruitment, assessing eligibility, and follow-up is similar when assessing different intervention groups. The flexible nature gives the ability to maximise recruitment opportunities for patients who are eligible for only a subset of the intervention options according to the eligibility criteria specified for each intervention arm. A growing number of interventions added to the platform will lead

to more eligibility criteria being added to the existing list, and could increase the time to assess a patient's eligibility to the study. However, with increasing change and complexity there are then challenges in conveying these accurately to primary care staff who may be unfamiliar with the platform and other more complex study designs.

The perpetual and flexible nature of the platform design requires good communication to both the GPs and patients before trial set-up. In particular, the trial team needs to inform all GP practices as soon as a treatment is dropped from the platform. On the other hand, when a treatment arm is added to the platform, all necessary documentation should be sent to all sites with any appropriate training in a timely manner. Therefore, a clear communication plan at trial set-up, as well as continuous training sessions to GP sites when there is a protocol amendment, would be helpful to ensure effective communication and delivery throughout the trial.

Platform trials require many iterations of protocol amendments due to the ongoing adding and dropping of treatment arms. Depending on the speed of the recruitment, this could add pressure to the sponsor, regulators, and ethics to have a quick turnaround time to review and approve the amendments. There would also be an expectation of the recruiting sites to adapt the amendments as quickly as possible.

10. Research Delivery

10.1. Background and Rationale

While the scale and pace of the delivery of the PANORAMIC study, and the requirement for participants to receive and start medication (if so randomised) within five days of the onset of symptoms, presented a challenge for primary care providers, the NIHR CRN, and Devolved Administration (DA) colleagues, it also provided an opportunity to 'think outside the box' when considering recruitment and delivery models, to devise novel approaches, and to work collaboratively at a local and national level to ensure successful delivery in the context of a rapidly changing and dynamic pandemic.

The model agreed in the original PANORAMIC protocol was that "potential participants can be referred to Hubs by other healthcare facilities for possible inclusion". To further develop this potential model, and support the delivery of this complex community-based clinical trial platform in which medications were to be taken at home by the participant following a positive COVID-19 PCR or LFD test, an initial review of recruitment models used by other oral antiviral studies was conducted by the NIHR CRN team.

10.2. Developing Recruitment Models, and Scoping Exercise

An internal review of the recruitment methods used by existing studies was carried out by the NIHR CRN. Of the 12 NIHR CRN portfolio studies assessing antiviral medications between March 2020 and September 2021, 3 utilised primary care-only models, with 2 operating within the community care setting, and 7 in secondary care. A variety of potential recruitment options were used in studies across primary care, to maximise engagement and retention, and while it was initially thought that recruitment would be led by individuals presenting at a participating GP site, this became less likely as the pandemic progressed and GP practices were still operating total triage rather than seeing patients face to face, as advised by NHSE.

As a consequence of this review, approaches employed in other studies were explored for PANORAMIC, including:

- The use of Participant Identification Centres (PICs) within a primary care Hub and Spoke model.
- Engagement with Primary Care Networks (PCNs).
- Linkage with NHS Test and Trace to access information regarding COVID-19 positive individuals who had consented to be contacted regarding research.
- Linkage with the NHS 111 service and the COVID-19 specific 119 service, and COVID-19 Clinical Assessment Service (CCAS) in the height of the pandemic, in order to highlight research opportunities to service users.
- Linkage with research support services and established digital identification systems, to aid searches of patient databases to identify potential participants.
- The subsequent direction/signposting of potential participants to study websites for further information and to express interest.
- The use of media/social media and other advertising materials (e.g. study materials and posters being displayed in pharmacies and at COVID-19 testing centres).

It was noted that 'success' had been mixed across these models, with key learnings including:

- The need for considerable time and staffing, as many models were resource-intensive, with a need to review and follow-up lists of COVID-19 positive cases daily to maximise recruitment opportunities and enable intervention within five days of symptom onset.
- The use of practice-to-practice PIC models required resource-heavy engagement and relationship maintenance. Success was dependent on practice type, with linkage with 'red' or 'hot' hubs (practices seeing individuals with COVID-19, or patients with symptoms, face-to-face) working better for some studies than other GP PICs.
- Linkage with NHS Test and Trace was challenging to set up.
- The conversion rates (number of individuals contacted versus the number enrolling) was variable, but often low:
    - potential participants may be more receptive if the follow-up contact is from a local GP site, rather than from a national team (which may feel like cold-calling).
- Database searches required a clearly defined follow-up process, with appropriate infrastructure and relevant regulatory approvals. Having this in place in advance, with all aware of the steps involved in the pathway (post-search), was noted to be important in maintaining engagement with potential participants.
- An ability to flex recruitment strategies in response to the changing COVID-19 landscape was important to maintain momentum and maximise opportunities.

10.3. The Use of Hub and Spoke Models

It was recognised that there was limited pre-existing infrastructure in primary care to support the delivery of complex research at this pace and scale. As such, it was felt to be key to build on learnings from other COVID-19 studies delivered in primary care, including PRINCIPLE.

PRINCIPLE initially recruited participants from selected research-active GP practices across the UK, but as the pandemic progressed the provision of clinical care was delivered in an increasingly remote fashion in general practice and the study developed into a decentralised study allowing patients to remotely self-enrol into the trial, either via the trial website or over the phone with the trial team. Once patients had registered and consented, the GP would check eligibility before randomisation, and it was felt that this decentralised approach made participation as simple as possible for patients (Masoli, et al., 2021), benefitting recruitment rates and improving accessibility. However, whilst a Hub and Spoke model was proposed by the study team and NIHR CRN in order to bolster recruitment to PRINCIPLE, this was not ultimately used. The key reasons for this were concerns over competing demands of the available workforce, concerns about the expected inclusion of intravenous or intramuscular agents in the protocol, and the requirement for home visits - all of which would have been challenging in primary care in the pandemic.

This experience with PRINCIPLE allowed the opportunity to co-create with the study team and develop national models of delivery in primary and community care, while utilising 'intelligent recruitment' methods to follow the COVID-19 incidence data at local and national levels.

PANORAMIC gave an opportunity to 'road test' and refine the use of a Hub and Spoke model in a real life study setting, providing the chance to fine-tune the model throughout (Tonner, et

al., 2023). By working closely with the PANORAMIC study team a complex Hub and Spoke model was developed *alongside* an established decentralised study design.

For the PANORAMIC study, a Hub was defined as:

- A GP Hub: a single GP Practice or PCN(s)/Federation or various combinations of these.
- A 'non-GP' Hub: a Community Trust, Acute Trust or other NHS service.

Here, Hubs acted by definition as the research site, and along with their associated Spokes, identified patients in their practice populations with positive COVID-19 tests (PCR or LFD); approached participants for eligibility and/or consent within 24 hours of positive test result being received; and undertook all study procedures (as detailed in the study protocol). At each Hub, a GP, research nurse or other healthcare professional completed daily screening, baseline, informed consent and eligibility review. The use of Hubs allowed additional safety monitoring visits or phone calls, where required by the Intervention Specific Appendices (ISA). A PI at each Hub provided trial oversight for participants recruited.

A total of 70 Hubs were identified to participate in PANORAMIC, across all four nations of the UK. Hubs were selected by the study team (in collaboration with NIHR CRN and DA colleagues) dependent on the size of the population base; a track record of successful recruitment into CTIMP and non-commercial COVID-19 studies; geographical proximity to Agile teams; and willingness to undertake study procedures (Day 1 and Day 2 safety calls, Serious Adverse Event monitoring during the 28 day follow-up period, and conducting the virology sub-study for each agent).

Hubs were able to use Spokes - GP practices or 'non-GP' sites - within the geographical area, assuming all Spoke practices could operate under a single site agreement with a Hub PI. Spokes functioned as 'referral centres' and undertook screening activities daily, contacting identified participants to notify them of their referral to the Hubs. The use of this model allowed for broadened access to the study across wider geographical areas with larger populations, often whole cities or counties, allowing research to be brought to the patient. Rather than using traditional PIC referral, these Spokes used clinical referral.

Although contracting in primary care is regarded as less complex than that in secondary care, lessons were learned from the PRINCIPLE study and discussions were held at an early stage to ensure smooth site set-up. This included close working with the Sponsor to ensure contracts were pre-signed by the University of Oxford, resulting in fully executed contracts upon practice signature. This streamlined set-up activities, allowing for expedited site greenlighting. Discussions with the Health Research Authority (HRA) were also undertaken at an early stage to understand contracting requirements - alongside eligibility checking and Good Clinical Practice (GCP) requirements - which simplified arrangements for participating practices through the development of streamlined agreements.

10.4. Adaptation of Hub and Spoke Model to Local Practice

A number of diverse Hub and Spoke models were used across the UK, reflecting the need to embed novel recruitment models into local practice with flexibility. In response to a stock-take

survey requesting information on local Hub and Spoke configurations, 39 responses were received by 11 January 2022, which revealed:

- 13% of practices were operating as single sites only.
- 87% of practices were operating within Hub and Spoke models (of which, the number of Spokes ranged from 1-32).
- Population coverage ranged from 7,870 to 400,000 patients per Hub.
- Total population coverage was approximately 3,250,000 patients, equating to 6% of the English population.

In addition to the use of Hubs and Spokes, a centralised recruitment system was developed and deployed by the central study team, similar to that used in the PRINCIPLE study. Individuals with a positive COVID-19 PCR or LFD test were able to register their interest in the study through the PANORAMIC trial website with eligibility determined via a self-assessment questionnaire online. These participants were then contacted and consented by the central study team including clinical colleagues, supported by Agile teams in the local networks and additional staff identified by the NIHR CRN. Individuals self-referring to the PANORAMIC website in Wales were contacted and enrolled by the Public Health Wales (PHW) team. It was reported by the study team that the use of the summary care record (SCR) was very helpful in terms of offering access to the patient record and assessing eligibility and then offering care within the trial as part of this centralised model.

In order to better describe the flexibility and adaptability of the Hub and Spoke models used in PANORAMIC a number of case studies were collated (see below) :

Case Study 1: OneNorwich Primary Care Network

OneNorwich is a large PCN spanning the whole of Norwich city, with over 250,000 patients. Organised into neighbourhoods, it includes both research-active sites and others (particularly in deprived areas) which had not previously engaged in research. Strong support from CRNEast of England, direct communication from the combined leadership team, and financial agreements enabled the PCN to be stepped up at speed. A structure in which all research-active practices within the PCN operated under a single-site contract, which reduced the burden of contracting, was also felt to be very beneficial within this PCN.

OneNorwich was the highest recruiting site to PANORAMIC, enrolling over 800 participants. Whilst practices within the network received COVID-19 positive patient lists directly at the start of the study, an early focus was on implementing the NHS Digital (NHSD) Population Health Platform, or WebViewer, across the network as soon as possible (see Section 11 for further information). Potential patients, once identified using the WebViewer, could then be assessed by research personnel across the PCN using SystmOne (GP clinical system) under a model supported by both Control of Patient Information (COPI) and the extremely engaged Primary Care Locality Manager who arranged for all-staff SmartCard access. The contribution of NIHR CRN nurses - searching for potential participants, screening patients for eligibility, and accessing all patient notes across the region as per data access contracts put in place by the LCRN - was also highly commended, as was the activity of the single EMIS (Egton Medical Information Systems, another primary care electronic patient record system and software)-using Spoke, who conducted searches and shared patient details with the wider PCN team.

CRNEast of England felt that PANORAMIC was deployed at the right time - as other work had slowed, staff capacity was increased, and other locality teams were able to offer support. The integration of the local Integrated Care Board (ICB) Research and Development (R&D) team, as well as the availability of the newly created Agile team, allowed a pooling of resources, to further support delivery.

Through the PI's outreach to other GPs, the NIHR Associate Principal Investigator Scheme which bolstered staffing, and the persistence of the LCRN team, local interest grew during PANORAMIC, empowering the less research-active sites to participate and develop. This resulted in increased primary care engagement in the region, and the inclusion of the less active sites under the broader OneNorwich contract. This has left a lasting legacy, including:

- Widening the number of research-ready practices in more deprived areas;
- Promoting whole-PCN working (rather than sites wishing to act autonomously);
- Giving regional flexibility as sites now feel able to rotate between and 'share' studies.

Case Study 2: Lancaster Medical Practice

Lancaster Medical Practice, part of the Morecambe Bay Collaborative, is a large practice with over 60,000 registered patients. The practice acted as a Hub, with Bay Medical Group practices (West End Surgery, York Bridge Surgery, and Westgate Medical Practice); Queen Square Medical Practice; and Ash Trees Surgery operating as Spokes for the molnupiravir arm of the study. The Hub and Spoke sites, which were already research active, covered a wide geographical area, and already had embedded NIHR CRN infrastructure. Existing research infrastructure across the Hub and Spoke network meant no additional contract checks were required, and no letters of access needed, prior to participation in PANORAMIC.

The use of the NHSD WebViewer was central to the success of this practice. Practice staff found the tool simple to use - especially as SmartCard access to records was already in place across the Collaborative - and noted that it provided COVID-19 positive patients across a large geographical area the opportunity to participate in the study. By using the WebViewer, the time taken to determine patient eligibility was reduced, and it was felt that such systems for commercial studies would be particularly beneficial.

"Wouldn't it be great if all studies [used] a similar system?" - Senior Research Nurse.

Aspects of study design also simplified study delivery for the Lancaster Hub and Spoke collaborative, with centralised IMP storage and distribution avoiding the need for complex in-house drug dispensing models. Participants appreciated that the drug could be delivered to their door, while site teams felt that real-time results sharing (characteristic of platform trials) was hugely beneficial to maintaining engagement and encouraging site participation.

"PANORAMIC was how trials should run in Primary Care" - Senior Research Nurse.

Lancaster Medical Practice, and the whole North West Coast Region, enjoyed participating in PANORAMIC and feel that remote delivery models have developed significantly through the study.

Case Study 3: Greater Manchester

In the Greater Manchester region, two practices acted as Hubs - Barlow Medical Centre and the Middlewood Partnership. Both practices are highly research-active with a strong track record of study delivery. The Middlewood Partnership comprises four practices and operates as a PCN, with a list size of approximately 33,000 patients, and worked alongside Alderley Edge Medical Practice in a Hub and Spoke model. Barlow Medical Centre, a smaller practice with approximately 17,250 patients, initially operated as part of a Hub and Spoke model with a nearby research-active practice, but this arrangement was dissolved shortly after recruitment commenced due to identified capacity constraints and difficulties in coordinating referrals to the Hub site.

Such capacity constraints may have been related to the time the PANORAMIC study was launched; decreased capacity due to other commitments - e.g. the deployment of COVID-19 vaccines, the influenza season, other ongoing COVID-19 studies, and the broader reopening of the portfolio - meant fewer practices felt able to contribute. That many practices were only beginning to resume normal clinical activities further dissuaded participation.

Elements of the design of the PANORAMIC study were also cited as reasons for limited uptake within the region. Take-up of the preceding PRINCIPLE study in the Greater Manchester region was very strong. PRINCIPLE was also highly centralised, whereas PANORAMIC required greater practice involvement in screening, consenting, and treating participants. Furthermore, PRINCIPLE used only repurposed, licenced oral IMPs, whereas the initial assumption (ultimately mistaken) that PANORAMIC would investigate monoclonal antibody treatments (which would require patients to be seen in-person), led to uncertainty around deliverability.

Although monoclonal antibodies were ultimately never included in the protocol, it was felt that final confirmation of the IMPs to be used at an earlier stage may have encouraged a broader degree of participation in the region, and meant more sites would have felt they have capacity and capability to deliver PANORAMIC. Similarly, clearer guidance at an earlier stage around information governance (IG) requirements was highlighted as a potential lesson to learn, particularly when working with practices which did not have the established PCN-level involvement of Middlewood Partnership. The data protection requirements needed, the data sharing agreements required, and the unusual clinical referral pathway used in PANORAMIC all raised questions which impeded the onboarding of Spoke sites.

Though participation in Greater Manchester was lower than hoped, study set-up was found to be straightforward at the two participating practices, requiring little input from the LCRN.

Case Study 4: Carlisle Healthcare

Due to the geography of the region and its largely rural population, North Cumbria operates a unique, vertically-integrated primary care research model delivered by a team of five individuals funded by North Cumbria Integrated Care (NCIC) Trust. The team includes a research-focused GP (PANORAMIC PI for North Cumbria), the Head of Primary Care and Community R&D (HPCC2RD) at NCIC, and three research practitioners, and serves as the research personnel for 16 practices serving over 170,000 patients across Cumbria.

The team is not formally allied to a specific practice, but holds honorary contracts with all 16, which allows rapid set-up under one Clinical Trial Agreement and with one site visit and one point of contact. It also allows the team to operate research surgeries and access patient lists and care records without the need for additional checks or applications. This structure removes potential barriers to timely set-up and delivery, whilst the PI's role as a 'research GP' for the whole region allows full focus on the delivery of the primary care research portfolio. This understandably proved very beneficial for the PANORAMIC study, and resulted in the recruitment of over 260 participants from this region in two years.

For PANORAMIC, the PI had access to patient lists from all practices via EMIS, secured via remuneration of participating practices. Searches were developed by the PI and HPCCRD at NCIC (as local coding does not always fit national norms), and the PI contacted all potentially eligible patients to discuss the study and hold clinical discussions. During the peak of COVID-19, PANORAMIC was the sole focus of the PI and HPCCRD at NCIC, who were the only individuals on the delegation log in this network of Hubs and Spokes. While PANORAMIC was also open to recruitment in Hubs in West Cumbria, recruitment proved difficult in this area and so the North Cumbria PI picked up activities in Cockermouth to support recruitment, taking to the road to visit patients at home as needed.

This autonomous, devolved model was very successful in PANORAMIC, and did not need strong oversight or support, though Agile team staff were available as needed. The team was careful to balance workload to ensure no bottlenecks, and made the most of small resource given the challenges of securing practice access for additional members of staff. Given this limited resource, the centralised medication delivery system was appreciated by the North Cumbria team as this decreased the need for travel, while access to positive PCR and LFD COVID-19 tests on EMIS removed the need for the team to attend local COVID-19 testing sites. The study was also appreciated by participants, who wanted access to antivirals and liked the opportunity to receive this at home with no need to travel to their GP practice.

Taking part in PANORAMIC was a positive experience for the team and participants, though some participants expressed dismay that if randomised to the control arm, no placebo was received, and the team felt that questions around the estimated glomerular filtration rate requirements for participants in the Paxlovid arm were never entirely resolved. During the transition from molnupiravir to Paxlovid, high workload in the central team led to challenges in query resolution, though the flexibility of the protocol was seen as a factor in the success of the study. In all, the PI and the team felt the design of PANORAMIC benefitted their participation. "*PANORAMIC fits the model, and the model fits PANORAMIC.*".

10.5. 'Research Ready' Pharmacy Constraints

One challenge identified in the set-up stages of PANORAMIC was the lack of access to trial pharmacies within primary care sites and the wider community. This led to some slight delays in set-up, with few selected Hubs identified as suitable to take part having suitable pharmacy facilities. At the beginning of the study, the expectation was for GP practices and/or their associated pharmacies to hold, label, and dispense the IMP, but logistical constraints (in terms of storage space, staff capacity, and dispatch concerns) meant that this was not always achievable. This led to a central IMP distribution model being developed, in which IMP was couriered directly to the participant's home.

The use of courier services came with cost implications and concerns over IMP delivery timelines, leading to planning challenges for the central study team. A contract was established with a dedicated commercial delivery company and this was hugely beneficial. This centralised delivery not only eased IMP flow to the patient, but also enabled IMP to be labelled and dispatched on the same day, giving more flexibility to the CTU team given the variation in the number of IMP packs needing to be distributed each day. Although there were some issues with this model, the relationship with the dedicated commercial company enabled these to be minimised. Rapid delivery of the IMP to the patient enabled the study to meet its deadline of randomisation and commencement of treatment within five days of symptom onset.

However, the need for a centralised commercial company to deliver IMP highlights the importance of community pharmacy input from the very beginning of the study design stage. In future studies, engagement of community pharmacy stakeholders will ensure an appropriate method for IMP storage and dispatch can be agreed up-front, minimising disruption later. Early engagement may also present opportunities for community pharmacies to develop local systems to support this activity, allowing greater involvement in studies such as PANORAMIC, which would benefit the delivery of clinical research in primary care setting in the future.

10.6. Employing Improved or Novel Recruitment Strategies

Given the complex network of Hubs and Spokes deployed in the PANORAMIC trial, and the requirement for positive COVID-19 results to be identified within a short time frame to secure participant eligibility, the use of digital participant identification systems to search databases was felt necessary to support study delivery. Practices initially conducted screening activity to identify SARS-CoV-2 positive patients daily in their practice using the NIHR CRN Primary Care Research Informatics and Digital Environment Solutions (PRIDES) IT searches available for SystmOne and EMIS and distributed via the Thames Valley and South Midlands PRIDES site. A PRIDES search is an agreed and validated search of a GP database using EMIS or SystmOne, including the agreed protocol inclusion and exclusion criteria to identify a cohort of patients who could potentially be eligible for a study. It is downloadable from a centralised database for practices to self-serve, and can be used in multiple practices without broader amendment.

Following identification, patients could be contacted either by phone or by text. Based on experience with previous studies it was felt that potential participants would respond more favourably to direct contact by their own GP practice rather than a central call centre, and so this model was championed (further details regarding recruitment flow can be found in Appendix 3). The use of text messaging was unusual in this context, but incurred no breach of

common law duty of confidentiality. Processes were established for individuals who had opted out of consent-to-contact, to ensure text messages were not sent to these individuals. The wording of the text did not need to be ethically approved (though the message was reviewed by the ethics committee prior to use). Text messages were regarded as opt-out consent and, like telephone contact, were sent by the GP practice to increase the chance of engagement.

On advice from the HRA, it was noted that data sharing between GP practices (Hubs and Spokes) participating in the PANORAMIC trial could be for the purpose of clinical care, where such sharing was deemed to be needed for care purposes in the opinion of a relevant health care professional. That is to say, data sharing could occur without breaching the common law duty of confidentiality to enable patient access to a treatment option they would not otherwise have had through their own practice, even in the context of a research project.

This referral system (outlined in Appendix 3) was identified as a clinical referral, rather than a referral for the secondary purpose of research which may incur information governance and research governance issues. The use of this pathway was, to the team's knowledge, unique in infectious disease primary care studies, but presented numerous benefits, along with several challenges. Within the context of the pandemic this was particularly relevant as the only way that patients with mild-to-moderate COVID-19 in the community could access treatment was through the trial. High-risk patients, who were not initially eligible for the trial, were immediately referred to their CMDU in their local hospital. No formal data sharing agreements between Spokes and Hubs were required. Because the referral was for the purpose of care and not for the secondary purposes of research, Spokes did not need to be established as PICs, and additional patient consent was not required for the sharing of information between practices as this was conducted on the basis of implied consent for care.

In addition, the COPI notices proved a useful and unique adjunct to the need for reassurance for general practices and their linked data protection officers, allowing integrated working between Hubs and Spokes. Technically, clinical referral did not need approval through COPI (see above). However COPI appeared to open many doors for research and was considered by some GPs as a 'comfort blanket' for IG concerns - although there were a number of gaps in knowledge around what was and what was not required relating to COPI in study delivery. The COPI notices were a unique situation during COVID-19 and no equivalent would necessarily be available for other non-pandemic situations. It was also suggested that there was significant confusion around these IG issues in primary care and these were generally challenging. Further work to streamline information governance arrangements and share learning is recommended.

It is notable that Scotland and Northern Ireland did not operate under COPI; in Scotland, Public Benefit and Privacy Panel approval was required to allow this degree of data sharing, and there was no COPI or Public Benefit and Privacy Panel (Confidentiality Advisory Group equivalent) in Northern Ireland. Whilst this did not prevent the study successfully recruiting in these nations, alternative arrangements were required and slight delays were observed in sites becoming recruitment-ready. It was also observed that, whereas Hubs and Spokes did not require data sharing agreements, many practices felt that the establishment of agreements provided comfort, and so opted to employ their own data sharing agreements which once again

drew short delays. Notably, no COPI equivalent would necessarily be available for other non-pandemic situations in the future, and this must be taken into account for future studies.

10.7. Health and Care Engagement

As with other studies, e.g. RECOVERY, the desire to embed trials within clinical care was key to delivery. One particular strength of the delivery of PANORAMIC was the opportunity to link invitations to participate with the reporting by patients of positive test results. At the start of PANORAMIC, patients received an NHSE text once they registered their positive PCR or LFT (through NHS Test and Trace) indicating that they might be eligible for research but not specifically mentioning PANORAMIC. This was due to difficulties in sharing the University of Oxford website address in a text.

However, in March 2022, this issue was resolved, and PANORAMIC-specific texts were sent to patients registering a positive test, leading to a massive increase in recruitment and hits on the trial website. Similarly, in Scotland, Test and Protect (T&P, the Scottish equivalent of NHS Test and Trace) included a signposting message and link in the email notifying individuals of a positive test result. The link was to a microsite with information about studies including PANORAMIC that sought to to enrol those in the early stage of infection, with links to the study websites for more information about enrolment at this time. Recruitment to PANORAMIC was capped at 500 participants per day to maintain a feasible workflow and high enrollment.

In light of this, it may be prudent to consider whether research could be better linked to both symptomatic and asymptomatic mass testing programmes for future pandemics as well as widespread surveillance. It was also noted that when contacted by the NHS text platform, people felt secure and safe to respond. However, it is possible that signposting to an individual study, rather than a generic invite to pandemic research, could be more effective.

Engagement with NHS 111 (and previously 119) was explored in order to signpost patients to the trial. However, it was not possible to embed an invitation to research within the clinical care provided by out-of-hours teams. This is an aspect of pandemic care which could be better developed in future to overcome these challenges. However, this would need top-down messaging to NHS 111 and a mandate to deliver research in this clinical context. Similarly, it was felt that linkage with CMDUs could have been stronger, with fewer participants recruited than expected through CMDUs when patients were found to be ineligible for treatment through these services. Again, if a similar model is used in future pandemics, this should be developed and cross-referral encouraged. Appropriate and clear signposting between the trial and CMDUs would also be needed.

A particular area in which increased engagement would have been beneficial was the care home setting. PRINCIPLE recruited 1% of its total participants from care homes, while PANORAMIC enrolled only 261 participants (0.8% of total participants) from care homes. Although recruitment in care homes was feasible for PANORAMIC, complex contracting requirements and care home staffing and capacity proved a barrier to participation and so no care homes were set up as sites. Individuals recruited in this setting were either supported by care home staff to self-enrol, or were enrolled by visiting GPs during COVID-19 outbreaks.

Patient capacity presented an additional barrier; recruitment of care home residents with dementia required a letter of agreement from the next of kin or power of attorney, which would have proved difficult to obtain within the short turnaround time between a positive COVID-19 test and commencement of treatment. As patients lacking capacity could only be enrolled in care homes, and not in their own homes, due to the need for supervision when taking medications, few participants lacking capacity were enrolled. Due to these difficulties, care home recruitment was unfortunately not a viable recruitment strategy, and would need rethinking in a future pandemic. Depending on the characteristics of a future pandemic, there may be an urgent need to recruit in care homes. Future studies need to ensure they give due consideration to care home recruitment at an early stage.

10.8. Recognising and Recording Recruitment

In light of the recruitment models used in PANORAMIC, a novel mechanism for recording recruitment activity (RA) and Hub activity within NIHR CRN systems was required. In normal circumstances, RA is mapped to the location of participant consent, and where participants were recruited through Hubs in PANORAMIC, RA was mapped in this way. However, for central recruitment, it was felt to be important to be able to visualise participant location, to ensure geographical equity of access to treatment as part of the PANORAMIC study. As such, a novel approach was devised. While central recruitment activity was mapped to the point of consent (Oxford University, or PHW), the participant eligibility and consent form was created to include the postcode of the participant's GP. Collecting this information allowed the general location of participants within the UK to be identified (see Figures 2A and 2B).

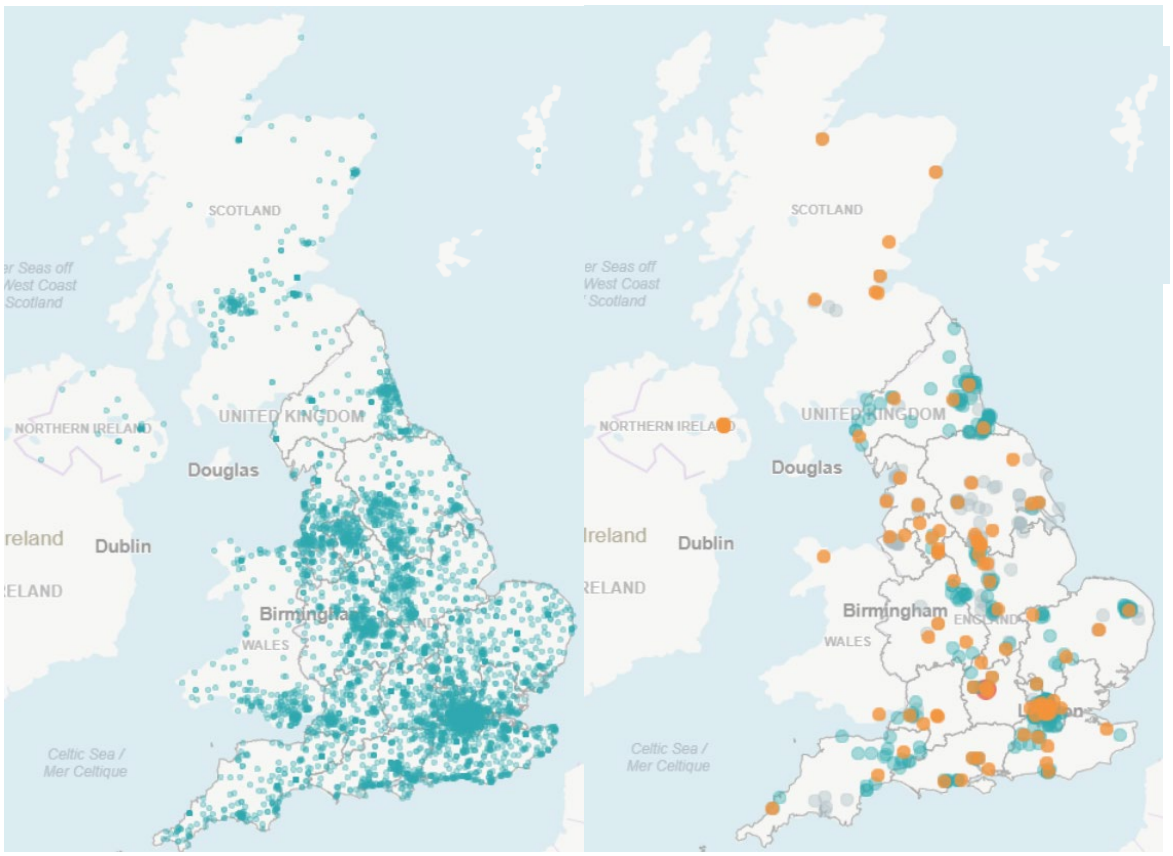

Figure 2A. (left) The location of participants recruited to PANORAMIC in the UK (using the postcode of the GP with which the participant is registered). Figure 2B. (right) The location of

Hubs (orange), Spokes (blue), and central recruitment sites (red) participating in PANORAMIC. These figures represent the final recruitment to the study (28 March 2024).

10.9. Staff Provision and Capacity

In light of the service challenges within the primary care setting during 2021/2022, ensuring sufficient staff capacity in participating Hubs and Spokes throughout was a key consideration of the trial team, who are themselves experienced in the delivery of research in the primary care setting. As such, the PANORAMIC protocol was designed to be flexible, to allow the study to benefit from the skillsets of the workforce within each practice (see Section 14).

For the molnupiravir arm of the study, for example, database searches and patient contact could be carried out by any clinical member of the practice team, with eligibility assessment and consent to be conducted by qualified nurses or general practitioners (later expanded by amendment to include qualified prescribing pharmacists). To bolster capacity, arrangements were put in place to allow cross-practice working within geographical regions, thereby ensuring sufficient numbers of colleagues with required skills were available in participating Hubs and Spokes to continue trial-related procedures during periods of absence. This ensured access to the staff needed to recruit to the study, and this was further supported by the deployment of NIHR CRN Agile teams at a regional level which saw the embedding of dedicated workforces with appropriate skills within general practice to ensure simultaneous delivery of PANORAMIC-related procedures alongside usual clinical care.

The use of the centralised recruitment model augmented this resilience and flexibility, enabling balance and the opportunity to flex approaches through the life of the study as needed, for example when the molnupiravir arm of the study closed to recruitment and the Paxlovid arm opened, and the use of PRIDES IT searches became more challenging. Centralised recruitment also allowed the study to continue recruitment during periods of staff sickness or shortage, as activity could flex between the two models employed, and permitted the recruitment of participants from a far wider geographical area.

However, while the pragmatism offered by the protocol, and the use of two complementary recruitment models, permitted the development of a scalable delivery model across the UK, PANORAMIC was not without challenges. For example, seven-day cover was required in Hub sites to ensure Day 1 calls to confirm IMP receipt and Day 2 safety calls could be carried out in accordance with the protocol. While practices were empowered to make local arrangements to support this, the Day 2 safety calls could only be carried out by GPs, and this led to some sites electing to only recruit participants on Mondays to Wednesdays, missing potential participants whose results were reported later in the week. This issue was less acute for participants enrolled using the centralised recruitment model, but did limit activity in general practice.

Lastly, it was acknowledged that significant time and resources were dedicated to approaching potential participants in Hubs and Spokes who did not convert into participants (though this varied between practices), which may not be feasible, scalable, or cost-effective under non-pandemic conditions. With greater time available, efficiencies could have been achieved through the use of technology, or using Hubs and Spokes for specific trial-related procedures

such as viral sub-study sampling. Alternatively, targeting additional workforce to the central team (if possible) may have been beneficial, though this may have benefited the Paxlovid arm more than the molnupiravir arm of the study due to the complexities of recruiting to Paxlovid.

10.10. Regulatory and Governance

The successful delivery of the PANORAMIC study was underpinned by excellent collaborative meetings and conversations between the study team, the sponsor and the joint regulators (HRA and MHRA). These were productive and timely, and the Oxford CTU is hoping to replicate this for future studies. In particular, the open line of communication with the HRA was key. The pragmatic approach of the HRA in the complex world of the pandemic was considered essential to the effective delivery of the study, when no study of this size or scale had ever been attempted before in primary care, and their advice proved critical in reducing concerns about data sharing and instigating a system of clinical referral between sites. This regulatory pragmatism allowed the wider NIHR CRN workforce to operate flexibly and facilitate recruitment into the study, without additional arrangements needing to be in place with their employing organisations.

There were some aspects of the decentralised method of delivery of PANORAMIC that caused concern to the study team. For example during the pandemic, not everyone was on site, and so-called 'wet signature' delays were common. Allied to this was the need for HRA confirmation of their expectations around remote consent in the pandemic context. Delegation logs and the use of remote signatures or electronic delegation logs during a pandemic situation should be considered and accepted (Mitchell, et al., 2023), but this proved tricky, and took time to unpick and resolve. The HRA is currently exploring this.

Other issues encountered during the delivery of the study revolved around the MHRA's views on the appropriateness of non-medical prescribers. This related more to Paxlovid than to molnupiravir and was due to the numerous contraindications to Paxlovid treatment. Only medical prescribers could prescribe Paxlovid initially, and this led to a need for more doctors to be involved, which in itself caused delivery issues as medical input was in short supply.

There was general agreement that the HRA needed ideally to unpick and publicise regulatory flexibilities, and identify immovable barriers, to ensure that sponsors are dynamic whilst not incorrectly perceiving that regulation is being diluted. It should be noted that these lessons learnt around regulatory requirements and governance are not specific to pandemic studies, and could be transferable to primary care studies and studies in other sectors/settings in non-pandemic situations. A statement from the HRA on current and future activities being undertaken to explore information governance concerns and provide greater reassurance in this space can be found in Appendix 4.

10.11. Funding and Costing Issues

The PANORAMIC study demonstrated several challenges with the organisation of costings and the arrangement of payment after its rollout in December 2021, during ongoing recruitment through 2022, and after the addition of the Paxlovid arm and cessation of the molnupiravir recruitment arm. These issues were exacerbated by the scale of recruitment to the study. A

summary of challenges encountered can be found in Appendix 5, with further details outlined in the following sections of the report.

10.11.1. Initial Preparation of the Costings for PANORAMIC

Initially the NIHR CRN worked alongside the CTU to prepare the SoECAT as per standard NIHR processes in order to correctly categorise the Cost Attribution of the costs against the categories of Treatment costs, Service Support Costs (SSCs) and Research Costs according to DHSC's AcoRD guidance. The cost attribution used the procedures known at the time of completing the protocol and was based on the best information available from the member of staff undertaking each activity (clinician or nurse). Separate templates were required for the treatment arm for molnupiravir; the standard of care arm; the two virology sub-study arms; and the intensive safety monitoring arm.

There were three principal areas of concerns that supported a separate reimbursement model:

- Insufficient payment for eligibility, additional time would be requested.
- Staff undertaking activity at some sites could include the GP rather than nurse and thus the costing rate is incorrect.
- Delivery modes included Hub and Spoke models, requiring a separate funding method.

The cost attribution was designed to be agnostic of the delivery method, i.e. whether central or via a GP practice. Although in primary care a SoECAT is often used as a costing template to determine payments, this is actually outside the remit of the SoECAT and given the scale of the study, an effective reimbursement model was derived using the initial cost attribution, and the use of the Summary Care Record by the study team greatly facilitated screening and eligibility checks of potential participants by the clinical team, without the need to review the individual participants' full GP record, and should be recommended for similar decentralised trials across all four nations. feedback from a variety of clinical and managerial colleagues. The payment was split between the Spoke activities (clinical referral and eligibility) and the full research activities for the Hubs.

10.11.2. Hub and Spoke Models and Costing

As discussed elsewhere, PANORAMIC used clinical referrals from Spoke GP practices as opposed to PIC referrals. Under the DHSC's AcoRD Guidance, valid SSCs for the identification of patients for a research study were payable since they fell within the framework of the 'research study'. However, in the case of PANORAMIC where clinical referrals were undertaken, this was not valid for payment under AcoRD, since clinical referrals are considered part of the activities a GP is expected to undertake within normal clinical practice.

A clinical referral is not supplemental to those activities conducted by a GP under their contract with the ICB and therefore should not be separately funded. Whilst this activity is undertaken for other studies, such as oncology studies, the scale of the PANORAMIC study magnified the 'additional' work that was perceived by the practices. To the team's knowledge, clinical referrals had not previously been used on this scale for a research study. The second activity undertaken was checking the eligibility of the patients who were going to be referred. Thus, in totality for the study the payment for eligibility was considered inappropriately low for the burden of

activities that were undertaken. A decision was taken to allow additional time for eligibility checking to partly compensate for loss of time in undertaking the clinical referral.

10.11.3. Spoke Payment Model

Different avenues were explored when considering the payment model for Spokes undertaking site-based activity. The payment needed to be seen to appropriately recompense GPs for participation in the study and to be variable, dependent on the number of clinical referrals undertaken and patients subsequently recruited by the linked GP Hub practice. It also needed to be flexible to accommodate the variation in Hub and Spoke models which existed across the country, from Hubs with a couple of Spokes to those with up to 40. A single monthly fee was considered inappropriate since it risked disincentivising those practices in areas of high activity and conversely inappropriately rewarding practices with little or no activity with a lower COVID-19 incidence. Models focused on payments of recruited patients arising from referrals were impractical due to the challenge of tracking this information.

A tiered model dependent on the number of recruits per month was considered the most appropriate, with a sliding scale of reimbursement for the eligibility and database checking. Individual Networks were charged with arranging mechanisms for monitoring the number of monthly referrals and to ensure that appropriate payments were made for practices in their region. It is recognised that the staff conducting Spoke activity varied significantly across regions, from activity residing in a central team to that being conducted in individual Spokes. Regions also varied in whether LCRN staff, practices staff or a combination was utilised for this activity, and thus the degree to which the funding should be passed to practices. Given the speed that the study was implemented it is considered that for future studies of a similar scale, care should be taken to avoid potential double funding.

Costings were shared as 'consultation in use' with regular discussion regarding their appropriateness. Whilst there was continuing concern around whether costs were sufficient from practices, and the long-term affordability of the funding structure, the reimbursement plan was maintained during the financial year 2021/22. Networks were able to maintain funding using underspends due to decreased numbers of studies running in the aftermath of the pandemic. For the financial year 2022/23, several LCRNs raised significant concerns regarding the continued affordability, and a range of estimates were produced. It was recognised that the personnel undertaking the activities in some recruitment models were Network staff and thus did not require additional funding.

Following the initiation of the Paxlovid arm, the costing framework was revised significantly, reducing payments to Spokes with a set cost of 30 minutes of administrative time per week and a fixed payment per patient referred to cover eligibility checking. Clarity was also provided that SSCs should be adjusted for practices depending on those actually incurred by staff and any research activities undertaken at practice level should be done on a cost recovery basis.

10.11.4. Limitations of SoECATs for Platform Studies

Through PANORAMIC, limitations were observed in the use of the SoECAT as a vehicle for undertaking the cost attribution and costing. Whilst the SoECAT is by definition not meant to

be used as a costing template, in reality it automatically produces values which are then commonly used to produce costings in primary care. There is then an expectation that these will be used without further modification. Though the SoECAT required revising for the Paxlovid arm, limitations were more generally observed due to the continuously changing nature of a fast-moving study and the variety of protocol deployment models in different settings, DAs, and Hub and Spoke networks. SoECATs assume that sites deploy the protocol in a consistent manner and that site activities are similar, but PANORAMIC allowed a high degree of variability in terms of centralisation of activities and the personnel who undertook them, resulting in a significant variation of costs incurred which was emphasised by the scale of the study. Moreover, thoughSoECATs can be modified following protocol amendments, it is not practical to continually implement and circulate in the same time frame for site operation.

10.11.5. Excess Treatment Costs

For PANORAMIC no Excess Treatment Costs (ETCs) were incurred; all drugs were supplied free of charge. However, future similar studies may incur ETCs and their payments may cause significant difficulties (further information can be found in Appendix 6). Whilst ETCs could be calculated initially, be recorded for the national payment system, and be altered should the dispensing mechanism or IMP supplied change, this would cause challenges with the recruitment and thus incur ETCs mismatch with the payment calculations and schedules. For future studies it is recommended that potential ETCs, and their frequency of variation, should be considered at an early stage, with a view to centralising the IMP supply activities and supply using the payment method 2 or 4 as described in the national DHSC ETC Process & Guidance:

- **Method 2:** ETC payments will be made to a single site or organisation irrespective of the sites that have uploaded recruitment.
- **Method 4:** The total ETCs incurred at a recruiting site will be paid directly to the intervention site.

10.11.6. Challenges Encountered in Payment of Research / Service Support Costs

The following challenges were also encountered during the delivery of PANORAMIC:

- **Differences between NIHR CRN and CTU research payment documentation:** The payment of research costs by the CTU (outlined in the contract) was based on different payments for patients on the active arm compared to the usual care arm, whereas the funding model proposed by the NIHR CRN outlined a single rate based on the 50/50 randomisation. Going forward, it is advised that the NIHR CRN engage with the CTU in advance to communicate a cohesive response.
- **Variation of Delivery Models across England and the DAs:** In reality, how the study was operationalised across the four nations varied dramatically and concerns were raised as to the appropriateness of some costings. While this is a valid concern, the decision taken was to maintain the costings and attribution at the same level for the DAs while accepting that local implementation may vary. To have variation in the costing model across the four nations would have introduced additional complications which would have been difficult to resolve and set an unwelcome precedent.

11. Digital Support and Engagement

11.1. Background

It was generally accepted by all stakeholders that the data-driven aspects of the delivery of PANORAMIC were a significant step change for primary care and augured well for the future of primary care research, particularly in large-scale nationally-important studies. It was noted that the learnings from the preceding PRINCIPLE study were important and had been further amplified in the PANORAMIC study itself, though IG and research governance issues occupied significant amounts of time and discussion. Organisations worked together to support data processes, and share awareness and understanding of each other's processes, in order to align activities to support data sharing and IG, which was most welcome and is discussed earlier in this document.

The learnings from the digital and data issues that arose during the delivery of the study are important and relevant to future trials, particularly in a primary care setting. These include the comparison of the cohorts identified by the WebViewer (see sections below) and those identified from clinical systems using the established PRIDES searches. It is possible that a similar approach using the WebViewer could be taken for future pandemics, though a number of dependencies would need to be addressed.

11.2. Data-Informed Identification of Participants

Recruitment of individuals across the country at the height of a pandemic led to new methods of identification, e.g. the PANORAMIC Population Health WebViewer, and consolidation of existing methods of recruitment in primary care research such as the NIHR CRN PRIDES service. For the PANORAMIC Population Health WebViewer, there were significant learnings.

11.3. NHS Digital PANORAMIC WebViewer

In late 2021, at the start of PANORAMIC recruitment, it was suggested by DHSC - in discussion with the NIHR CRN and the study team - that an existing NHSD platform, originally designed to identify high-risk patients with COVID-19 for the clinical deployment of antivirals through CMDUs, could be repurposed to facilitate the identification of positive COVID-19 cases in the community. Initially, in collaboration with the ATTF, a Use Case was discussed and agreed with NHSD, which included the definition of the Minimum Viable Product (MVP) for the first delivery of the WebViewer, resulting in collaborative working with NHSD to refine an existing platform for use as a recruitment tool for the study in England.

The existing NHSD platform was further enhanced to support recruitment to PANORAMIC by identifying potentially eligible patients, to allow research staff (in an NHS context and with suitable authorisation) to identify at a practice level who was potentially eligible for the study and contact them directly. This initial version of the WebViewer (see Figures 3 and 4) was delivered as a pilot, funded by the ATTF. It used a variety of NHSD data sources (see Figure 5) to identify potentially eligible patients for the trial, modelled on the inclusion and exclusion criteria of the PANORAMIC protocol, applied to patients who had recorded their positive COVID-19 test result on the appropriate result platform. It also enabled identification of potential participants across a number of practices, dependent on the appropriate

authorisation of research staff to access these data, in line with the Hub and Spoke delivery model of PANORAMIC.

The development and delivery of the WebViewer was in addition to the existing NIHR CRN PRIDES searches, which perform a similar function, but using health data available within the GP Electronic Health Record (EHR) to identify potentially eligible patients with positive test results. While the WebViewer was under development in the first months of PANORAMIC recruitment, PRIDES searches were used to support study delivery at that time.

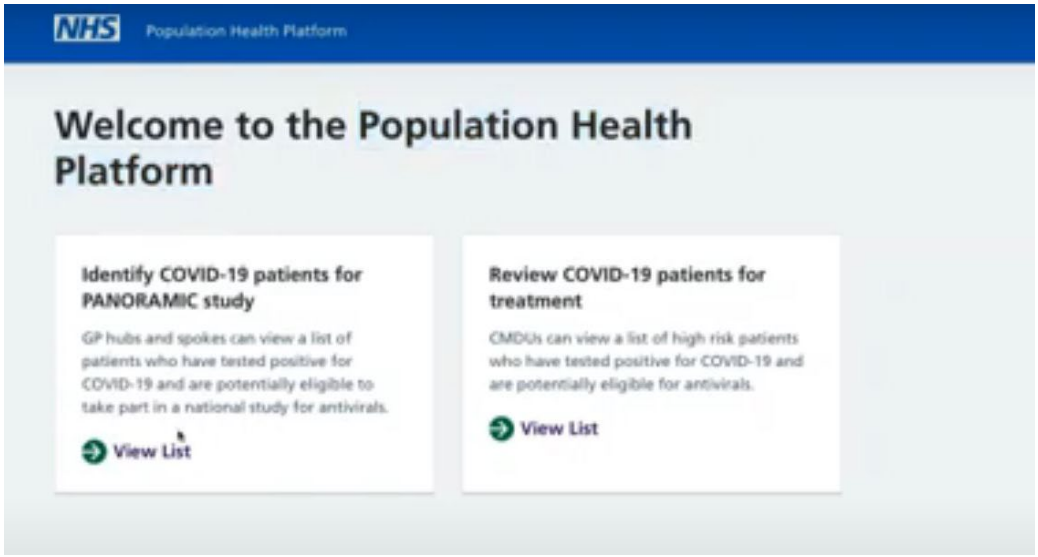

Figure 3. Screenshot of the NHS Digital Population Health Platform WebViewer.

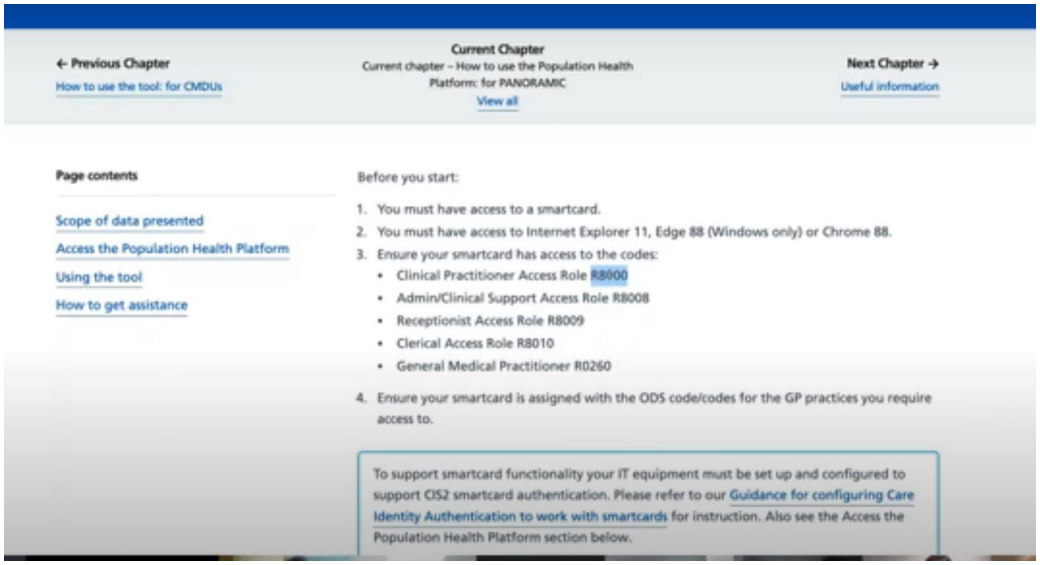

Figure 4. Screenshot of the NHS Digital Population Health Platform WebViewer instructions.

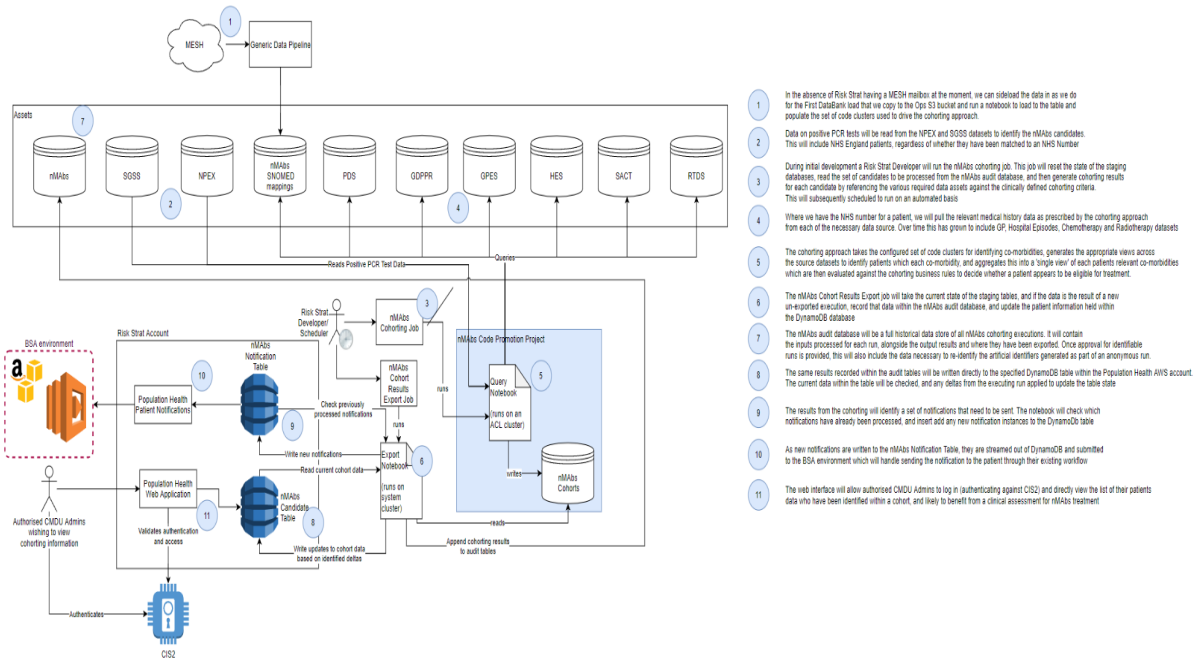

Figure 5. Data sources and complexity of rules leading to patient inclusion in the WebViewer.

11.4. Use of PRIDES Searches in Hub and Spoke Practices

PRIDES searches, developed by the NIHR CRN team over several years and refined for the PRINCIPLE study, were also used within PANORAMIC. While searches were made available for EMIS and SystmOne, searches for a third database system (Vision) were not, due to capacity constraints and the eventual availability of the NHSD WebViewer, potentially resulting in challenges for sites using Vision in the early stages of PANORAMIC.

The input of CRNWest Midlands, North East and North Cumbria, and South West Peninsula and their respective Digital leads was instrumental in the rapid design of PRIDES searches for the molnupiravir arm prior to launch in December 2021. CRNWest Midlands also generated flowcharts for identification of potential participants; their flow through the system, and their recording on the electronic medical record using the appropriate SNOMED codes (see below). It was generally agreed that there was a benefit from having a foundational PRIDES service which could be rapidly changed into new PANORAMIC-related searches. It was also relatively quick and easy to use the searches to identify potential participants as all the eligibility criteria were codable and hence could be validated and double-checked by the clinician engaging with the patient, through access to their individual EHR.

In addition, there was a desire throughout the pandemic to embed SNOMED research codes (previously developed by the NIHR CRN) into the GP patient record of all patients who were offered the opportunity to take part in research. This coding was further developed and implemented in PANORAMIC. A number of research codes with the attached CPMS ID for the trial were rapidly implemented as markers of engagement with the study (see Figures 6A and 6B). They also included a code for 'invited' or 'declined' which was found to be extremely helpful in the day-to-day management of contact with potential participants in sites.

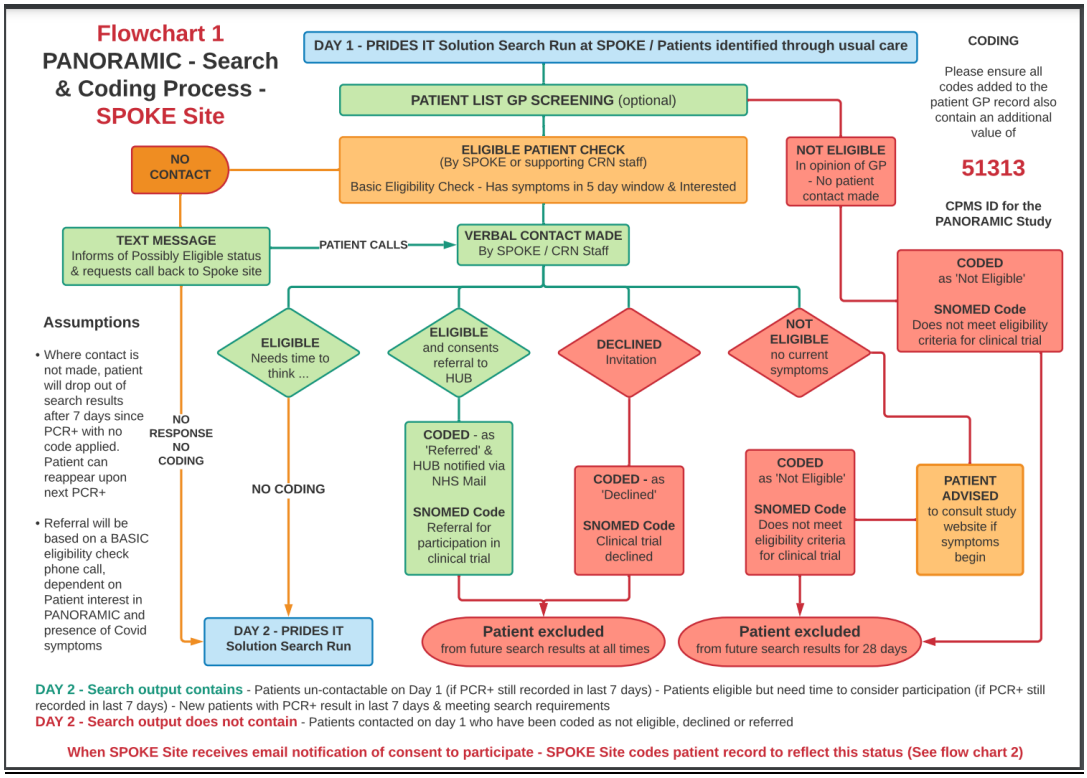

Figure 6A. Conducting daily searches using PRIDES IT to identify potential participants.

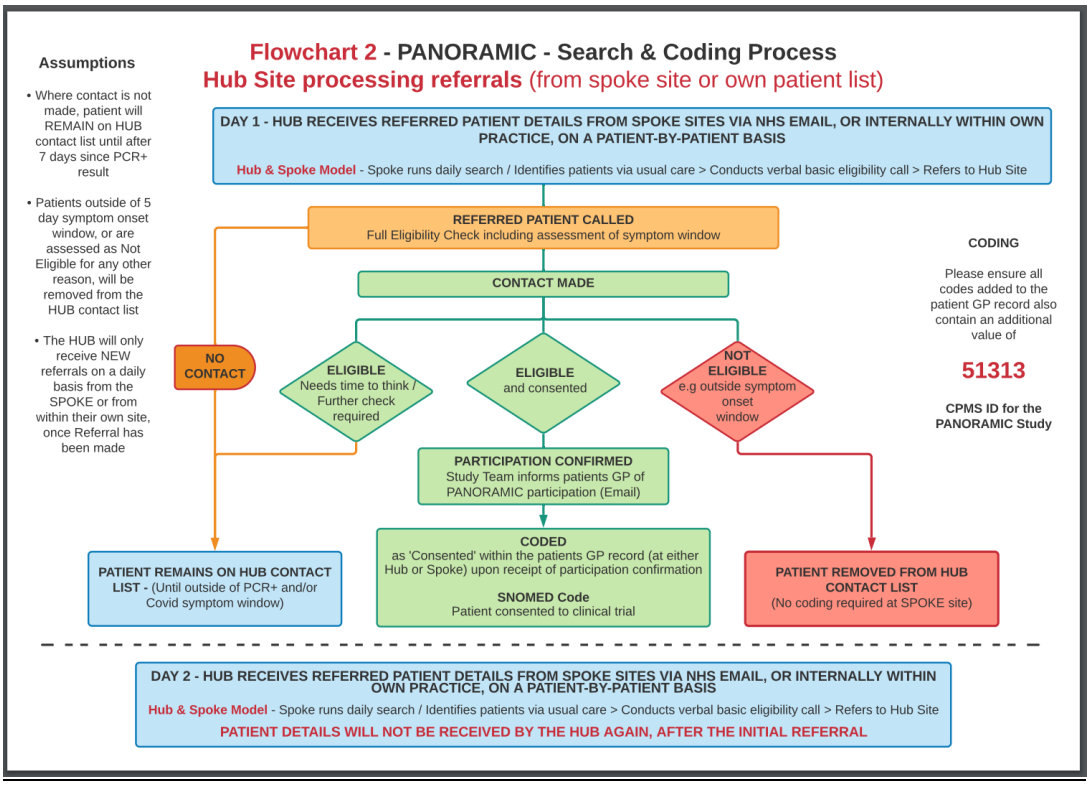

Figure 6B. Referral of potential participants to Hub sites for eligibility and consent procedures.

While PRIDES searches were set up quickly with a view to only being a temporary measure, further work was needed to maintain these as the study progressed. The searches were subject

to several alterations which were undertaken rapidly by the respective teams. The searches showed the benefit of a centrally agreed and version-controlled search for each computer system, held centrally on the PRIDES Thames Valley and South Midlands site. Cross-LCRN working helped to collate and distribute these searches, and in the regular weekly meetings with the study team and NIHR CRN core team, a standing PRIDES item allowed for feedback on the various searches and how they were performing in the real world to identify potential participants.

11.5. WebViewer: Opportunities and Perceived Benefits

Throughout its initial development, It was generally agreed that the WebViewer presented considerable opportunities. Initially, a benefits paper was compiled to summarise its key selling points to support the transition from PRIDES to the WebViewer upon its release (see Figure 7).

As an off-the-shelf product based on previous cohorts developed for the national flu vaccination campaign, it was relatively easy to develop, particularly as the existing cohorts paralleled the inclusion criteria for PANORAMIC. The concept of 'clinical referral', detailed elsewhere in this report, facilitated the underpinning of patient information within the trial and likewise supported the operation of the WebViewer, enabling sharing of patient information for the purpose of potential treatment for COVID-19 in this trial. Patients with presumed COVID-19 were encouraged to test and record their results on the WebViewer which was then pulled through into GP practice data. This also greatly facilitated identification of potential participants within the five-day window of recruitment from the onset of symptoms to entry into the trial.

NHSE reported that the PANORAMIC work had informed the development of DigiTrials and their recruitment service to support clinical trials. It was also stressed that the development of Secure Data Environments (SDEs), currently in the development phase, could be an important recruitment tool in the future for similar studies if they were able to use primary care data.

Access to the WebViewer was via dedicated NHS Smartcards for each individual accessing patient data. Whilst in some Hubs it was possible for practice staff to access data from multiple practices, in others it became very difficult to implement when it became clear that there were a plethora of access codes. For Hubs that delivered successfully using the WebViewer, e.g OneNorwich, the opportunity to recruit across a large number of practices using the WebViewer in a single PCN made it far more efficient (see Case Study 1).

The WebViewer was finally decommissioned at the expiry of COPI in July 2022, but by April 2022 it had been effectively decommissioned within the trial as it was unable to support the complex searching needed to deliver the Paxlovid arm of PANORAMIC. A bespoke search and WebViewer for this specific arm was therefore never developed, although at least one site still found the unaltered search useful enough to identify potential participants. However, the NIHR CRN PRIDES service was able to generate these complex searches.

Benefits of using the platform

These include, but are not exclusive, to the following:

1. Results are **refreshed 3 hourly** during the day, giving up-to-date and accurate data on eligible patient cohorts specific to each practice - without the need for further searches from the practice.
2. The platform clearly identifies those patients who **are early in the recruitment** window and who could be prioritised and contacted first.
3. The platform includes positive results from **pillars 1 and 2** of PCR and reported lateral flow testing (LFT).
4. If the patient declared their **symptoms start date** when being tested, the data are shown in the platform. This will help to streamline participant recruitment and reduce unnecessary screening.
5. A number of actions will be recorded in the platform to replicate the existing **flowcharts of activity** within hubs and spokes and the clinical recording required for patient records. These include "not actioned", "not eligible", "declined" or "referred to trial hub". These actions should be easily recorded for each individual patient and stored within the platform - although individual patient records will need to have clinical SNOMED codes added separately.
6. Patients in high risk groups eligible for the deployment of antivirals including **nMABs** are **excluded** from the platform searches. This will remove inadvertent double contact by the trial and the NHS.
7. The platform is designed to be **adaptable** to any changes in eligibility criteria as the study progresses - which will be addressed by NHS Digital colleagues rather than primary care IT colleagues across the CRN.
8. It is envisaged that the platform will efficiently enable a single hub to identify positive patients **across a number of other spoke** practices and then contact patients directly. Where staff are already using smart cards to access practice data, these staff may be able to use the platform with little or no changes to their smartcard access. The use of the platform will therefore facilitate efficient scale-up.
9. It is proposed that these data collected by the platform are used as the basis for **funding clinical referrals** from LCRNs to GP practice hubs and spokes, within the context of the trial - according to the costing mechanisms.
10. Users are informed that if they are having issues with the service, to contact their local IT support service. For other queries, NHS National Service Desk can be contacted at ssd.nationalservicedesk@nhs.net

Figure 7. Proposed benefits of using the NHS Digital WebViewer Platform.

11.6. WebViewer: Challenges

Ideally, there would have been engagement with the GP system suppliers and integration of the WebViewer into the patient's EHR systems placed within the practices. However, when the MVP was produced in December 2021, there was not enough time to implement it into the various GP systems. For some GPs and their teams, this was perceived as a distinct disadvantage, meaning that they needed to log into, and update, both a standalone platform as well as their clinical system. This duplication of activity was considered counterproductive; one of the main benefits of the WebViewer could have been the avoidance of dual entry of eligibility decisions where the decision was being recorded in both the WebViewer (as an 'action') and in the GP system (using the same clinical coding as a patient identified via the PRIDES searches). This should be considered in future development. In addition, future iterations of this type of approach should ensure that there are effective methods to prevent re-contact. There was significant concern about the risk of contacting potential participants more than once through the WebViewer, while coding of patients who had already been approached was easily undertaken through the PRIDES system.

GP reluctance to use the WebViewer was never fully resolved as the components intended to improve GP efficiency and make recruitment less time-consuming were never introduced. In

addition, the NIHR CRN team was unable to monitor engagement with the WebViewer, as the number of practices using the WebViewer and participants recruited were not available due to IG concerns. Some of the core benefits of the WebViewer were therefore not fully realised.

Further, major revisions, such as that needed for the Paxlovid arm, could not be undertaken, further inhibiting its rollout. In contrast, NIHR CRN IT specialists with experience of working with data from GP practices, generated PRIDES searches in a remarkably short time and contributed significantly to the delivery of Paxlovid from April 2022 onwards, further reinforcing the use of PRIDES for PANORAMIC. As a result of these challenges, a large number of sites indicated that for future deployment of such a platform, it would need to be designed from scratch and be able to respond in an agile fashion, rather than using an off-the-shelf, repurposed platform.

Lastly, the uptake of the WebViewer by the Hubs in PANORAMIC was disappointing, with only 3 of 65 Hubs (4.6%) self-reporting their use of the WebViewer, with the remaining sites using the PRIDES searches for either SystmOne or EMIS. However, the WebViewer did underpin the delivery of the study in those sites including the most successful recruiting Hub (OneNorwich). In total, 18% of Hub and Spoke recruitment in England (1,305 participants of a total of 7,070) was achieved by the three sites using the WebViewer (see Figure 8).

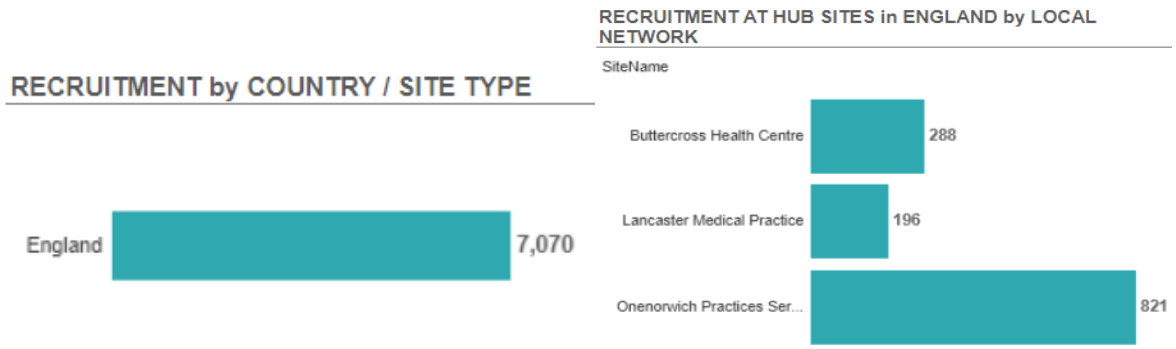

Figure 8. Final recruitment activity of the Hubs (right) which utilised the WebViewer, compared to overall Hub recruitment activity (left), as of the end of March 2024.

11.7. Recommendations for Future Studies using an NHS Digital Cohorting Platform

Each study, and even each arm, may need to independently determine the exact definition of the cohorting in the WebViewer for that study. As the WebViewer is used to identify *potential* participants rather than to support more detailed pre-screening / screening, the alignment of the cohorts to a study's inclusion / exclusion criteria could be quite loose - as long as the WebViewer saves time overall in recruiting for the study.

As NHSD will have the greater knowledge of their available data sources, and the NIHR CRN (with study teams) will have the greater knowledge of study-specific criteria, cohorting definitions are likely to come from collaboration between the parties. Given that each study has its own inclusion and exclusion criteria, future use of the WebViewer may need to be based on broad cohorting rules, or rules that can be easily configured for each study, to avoid requiring a new development project for each study using the WebViewer.

11.8. Text Invites to Potential Participants

Another significant development in PANORAMIC was the use of texting by participating practices to potentially eligible patients identified by these EHR searches. This was in addition to the PANORAMIC-specific texts sent via NHSD, and was a cost-effective and rapid way for general practices to contact patients.

Previously there had been concerns about the use of texting in a research context but, immediately prior to the pandemic, these were allayed by the Information Commissioner's Office (ICO). A standard invitation text was agreed with the HRA, who worked in close collaboration with the study team and NIHR CRN throughout the study and were particularly helpful in assuaging research governance and IG concerns around this, and other aspects of the study.

The ability, once fully realised, to text the patient directly with a link to the PANORAMIC website upon reporting a positive COVID-19 test result, was also one of the key aspects of the delivery of PANORAMIC that will inform future pandemic research, and was achieved via close collaboration of the study team with NHSD initially under COPI, but latterly under a section 251 agreement.

11.9. Data Sharing Issues as Part of the Trial

There has been an increasing use of routinely collected healthcare data for outcome data in clinical trials. In PANORAMIC, outcome data were collected from participants directly, but also through data linkage. However, significant challenges were reported when applying for data linkage across the four nations due to diverse legislation, sharing policies, and data structures. As mentioned earlier, straightforward measures such as including appropriate authorities in the study submission for all DAs should be ensured to remove such barriers.

Additionally, while routine clinical data retrieval for patient follow-up was achieved, it was perceived as being difficult and costly. It was suggested that large national GP datasets could be used for this in the future but would need to be streamlined for future primary care studies.

One requirement common to all four nations was having an established IG framework within an institution that meets data protection requirements. A Data Protection Impact Assessment (DPIA) with a detailed data flow diagram was required to ensure clear data sharing and flow during the trial. Specifically, onward sharing of NHSD data was highly restricted unless specified in the Data Sharing Agreement. For this reason, what data will be shared and with whom for what purpose, e.g. the safety data to the Data Monitoring Committee, should be made explicit in the application and the data flow.

12. Research Inclusion, and Supporting Equity in Clinical Research in PANORAMIC

12.1. Background

It is now well acknowledged that underserved communities are traditionally underrepresented in clinical trials. This includes research not happening in areas of high disease burden (Bower, et al., 2020), within ethnic minority communities (Redwood and Gill, 2013; Treweek, et al., 2020; Murali, et al., 2023) and those of other protected characteristics such as advanced age and gender (Goodwin, et al., 2023; Watkinson, Sutton, & Turner, 2021; Gahagan, Gray, & Whynacht, 2015). Evidence suggests that some of these same people were most likely to have severe-morbidity and mortality associated with COVID-19 (Williamson, et al., 2020; Khunti, et al., 2020; International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC), 2020., for example, death rates from COVID-19 were higher for Black and Asian ethnic groups when compared to White ethnic groups (Public Health England, 2020) and these groups experienced the virus more severely and had more adverse health outcomes.

The inequities that were well demonstrated in the COVID-19 pandemic were an important driver for this Equality, Diversity, and Inclusion (EDI) work to ensure that any COVID-19 trials in primary care addressed these inequalities. Lower participation rates are often due to a complex mix of the following:

- Cultural barriers (Witham, et al., 2020; NIHR, 2020) including inappropriate and ineffective communication about studies.
- Difficulty or inconvenience in accessing the study itself, e.g. site or website (Kapadia, et al., 2022).
- Religious and cultural beliefs, attitudes and behaviours affecting involvement in research (Skea, et al., 2019).
- Mistrust (Kadambari, et al., 2021, Witham, et al., 2020) and previous negative experiences of research.
- Systemic factors that exclude some underserved communities (Powell., et al., 2022).
- Minimal co-creation of messaging and engagement strategies.
- Lack of awareness of research in different communities (Healthtalk (DIPEx), 2022).
- General lack of understanding of what clinical research and participation entails.

Increasingly there are ways that this inequity can be addressed, particularly in a primary care setting and specifically for ethnic minority communities (Dawson, et al., 2022). The right trial design (Goodwin, et al., 2023) and setting, such as primary care, including pharmacy (Wilkinson, 2023), are important factors for success.

The PANORAMIC study built on the success of the earlier PRINCIPLE study by intentionally working to ensure that recruitment was representative of the wider UK population, specifically in terms of deprivation and ethnicity. Professor Mahendra G. Patel, a leading pharmacist with significant experience of working with Black, Asian and minority ethnic communities, was employed by the study team to engage underserved communities. These included people from ethnically and socioeconomically diverse backgrounds.

12.2. Engagement Methods to Support Inclusion

As part of this engagement, the PANORAMIC study team identified a number of innovative and wide-ranging opportunities to increase equity of engagement with potential participants in PANORAMIC, and a variety of recruitment strategies were initiated:

- Working with a broad range of ethnic minority communities.
- A community outreach strategy to develop UK-wide relationships with community, religious and faith groups (including places of worship).
- Gathering local and nationwide support from ethnic minority leaders from within their communities, health sectors, and through their respective organisations.
- Student outreach initiatives developed through collaboration with universities situated in areas of high deprivation and ethnic minority communities, with staff and students as advocates.
- Engaging national and regional healthcare institutions and organisations.
- The trial was promoted in English and multiple other languages, via local and national media channels and social media platforms.
- A range of user-friendly and culturally-acceptable resources were developed using information leaflets and videos in different languages to help reach out to diverse audiences across all four nations (Wafa, et al., 2023).

12.2.1. Reaching Specific Audiences to Support Inclusion

- Gender: engaging in and presenting at a number of local and national webinars e.g. promoting on International Women's Day 13 March 2022 on platforms through social media; Women's History Month March 2022: British Bangladeshi Women: Past, Present and Covid; and on Twitter (now X).
- Ethnicity: Diabetes Nurse Specialists promoting the study to vulnerable and ethnic minority patients through their clinical practice. Equally, having nursing colleagues champion from different ethnic backgrounds including Nepalese, Filipino, and Indian.
- Age: engaging with older people in care homes and with the Enabling Research in Care Homes (ENRICH) network was particularly challenging for this study. PANORAMIC continued to build on the experience in PRINCIPLE and promoted the trial through NHS England and other routes, although due to the pace of recruitment this was not as well-developed as in PRINCIPLE. Although care homes were not set up as sites, the team was able to recruit participants using the buddy system included in the protocol.
- Learning disability: e.g. the team continued building on the PRINCIPLE experience of using videos developed by award-winning young advocates with learning disabilities (with lift and caring responsibilities), encouraging recruitment to clinical trials during COVID-19 (these were shared via the trial website and social media platforms). These advocates supported the EDI work but also the patient and public involvement (PPI) element of the study.
- Populations in areas of significant deprivation: e.g. developing resources through CRNNorth East and North Cumbria, with animations and videos to encourage people in an area of high deprivation to take part in research.
- Patient advocacy: e.g. having a member of the Bradford Hindu Council as a participant advocate.

12.2.2. Co-creation of Community Outreach Programmes and Engagement

- National and regional black and ethnic minority communities and organisations, faith groups and places of worship: including the Muslim Council of Britain (MCB), Neasden Temple in London as one of Europe's most influential Temples (see Case Study 5), Indian Muslim Welfare Society (IMWS), Bradford Hindu Council, Sikh Alliance of Yorkshire (SAY), National Hindu Students' Forum (NHSF UK), British Bangladeshi Women, World Council of Hindus UK, South Asian Health Foundation (SAHF).
- Health organisations: these included the British Islamic Medical Association (BIMA), British Association of Physicians of Indian Origin (BAPIO), UK Black Pharmacists Association (UKBPA), British Indian Nurses Association (BINA), Nepalese Nurses Association UK (NNAUK), Tanzania and UK Healthcare Diaspora (TUHEDA), Medical Association of Nigerian Doctors Across Great Britain (MANSAG), Muslim Doctors Cymru, national and regional Pharmacy chains including for example Day Lewis pharmacy, Boots UK Limited, IMAM Pharmacy and LloydsPharmacy UK, the Chief Nursing Officer for Wales, the Chief Pharmaceutical Officer for NHS England, and Royal College of General Practitioners (RCGP).
- Healthcare regulators: e.g. General Pharmaceutical Council (GPC) promoting through its *Regulate* newsletter to all its pharmacy registrants, as well as on its website and through its social media platforms - this is the first of its kind clinical trial research support at scale.
- An example flyer created to promote the trial can be seen in Figure 9, and a selection of videos can be viewed here: Community outreach — PANORAMIC.

CASE STUDY 1: Bringing medical science and faith together to support research participation

The partnership with the British Islamic Medical Association and the Muslim Council of Britain was unique and the first of its kind in that the flyer that was developed in conjunction with them quoted the holy Quran stating it was an act of humanity for Muslims to engage in research (see Fig. 8). This was promoted through their religious

https://www.phc.ox.ac.uk/news/british-muslim-organisations-support-panoramic-ahead-of-ramadan

through mosques UK wide. This was also heavily promoted during the Muslims' holy month of Ramadan.

Figure 9. Flyer created in conjunction with the British Islamic Medical Association and the Muslim Council of Britain promoting the PANORAMIC trial.

Case Study 5: Neasden Temple

Participation into clinical trials has been traditionally low among people from black, Asian, and ethnic minority communities. However, through the PRINCIPLE trial at Oxford for the early treatment of COVID-19, we successfully demonstrated recruitment to be favourable and representative of the national diaspora across ethnicities and people living in areas of high deprivation. This was published in *The Lancet* and presented as part of outreach work at the United Nations in New York in November 2022. This approach was replicated and refined in PANORAMIC.

Our community outreach work in part involved working closely with national faith groups, one of which included the BAPS Swaminarayan Temple Neasden in London, known to many as the most influential Hindu temple in Europe. Their dedicated support in helping to raise the awareness of our trials to its UK-wide Hindu followers was impactful.

We co-designed a short slide presentation about information around the PANORAMIC Trial in terms of who was eligible and instructions on how to join that was culturally acceptable to the 200,000-plus UK-wide followers of the BAPS temple.

Building good relationships with such faith groups and places of worship created huge opportunities regionally and nationally for improving health and health inequalities within the community, especially where the need was greatest.

12.2.3. Promoting UK-wide Awareness to Support Recruitment

Sharing with pharmacy colleagues and organisations across the four nations involving community pharmacy through the largest national and regional chains, as well as local independent pharmacies. A number of key stakeholders supported this, including the Chief Pharmaceutical Officers from the Devolved Administrations (including a webinar in Northern Ireland), Primary care Pharmacy Association (PCPA), the hospital pharmacy network, Community Pharmacy Wales, Community Pharmacy Scotland and Community Pharmacy Northern Ireland:

- Large national pharmacy chains such as Boots UK Limited, LloydsPharmacy UK and others including regional and small independent pharmacies, promoted the trial through their outlets and websites via posters (see Figure 10). These pharmacies, along with others, had a footprint throughout the UK and helped reach out to underserved communities including those living in areas of high deprivation.
- Having the GPC as a regulatory body for pharmacists and pharmacy technicians supported and encouraged pharmacy registrants to promote a UK wide clinical trial such as this. The GPC promoted the trial through their own social media platforms, their websites, and an information bulletin sent to registrants via email.

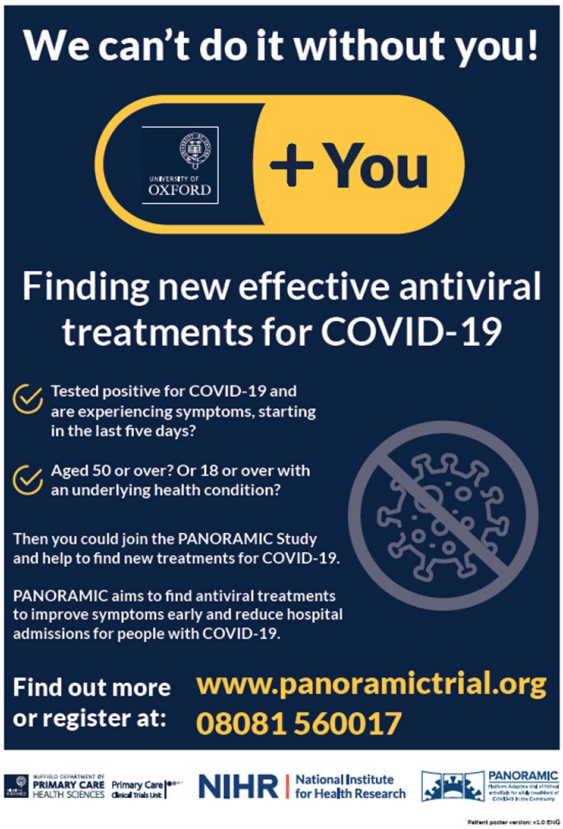

Figure 10. A typical poster displayed in pharmacies.

- Collaboration with universities located in areas of high deprivation and concentrated ethnic minority populations:
  - **Bradford University**: With Bradford having one of the largest concentrations of Pakistani residents in the UK, the team engaged with Bradford University. It supported recruitment through its press team and website by reaching out to students, their extended families and the wider community. This helped gain coverage through the local press and other news outlets within Bradford and to the wider Yorkshire region.
  - **Birmingham City University**: Birmingham is known as a 'super-diverse city', with 51% of its population being from Black, Asian or other minority ethnic groups. The team worked closely with the university and its senior staff to promote the trial through its student and staff community and via the university website and engaging its local press. The Vice Chancellor also produced a video to be shared through the trial website and across social media platforms.
  - **De Montfort University in Leicester**: De Montfort was the first university the study team engaged with, by reaching out to some of its senior academic staff within the pharmacy department to promote the trial. In addition, the team reached out through its pharmacy teaching and learning programmes and through its large south Asian and ethnic minority student cohort to help reach families and friends at home.
  - **The University of Bolton**: see Case Study 6.

Case Study 6: University of Bolton

Community outreach student initiative: targeting marginalised groups to help increase engagement with COVID-19 clinical trials

Introduction

The North West of England regularly reported high rates of COVID-19, with Bolton being one of its largest towns. It has a significant ethnically diverse population of Black, Indian, Pakistani, and Bangladeshi communities, who were disproportionately affected by COVID-19. It also has a university situated in the heart of the town. Recruitment to clinical trials nationally is typically low among ethnic minority and underserved communities. Through an innovative student-led community outreach programme, the team's aim was to help marginalised groups to be better informed about, and join, the PRINCIPLE and PANORAMIC trials in the search for effective community-based COVID-19 treatments.

Methods

The University of Bolton partnered with the trials' Inclusion and Diversity Lead to develop a 3-month student-led community outreach initiative. This involved empowering international students, from Nigeria, the Middle East, Europe and South Asia, to actively engage with the local communities in different languages to promote the trials. Induction training sessions with the relevant information were provided to the volunteering students, who spoke more than 10 languages collectively. They developed a suite of culturally sensitive resources about the trial including videos, leaflets and posters in these different languages. These were promoted through social media, the university's website, and in places such as markets, shopping malls, the North West Bolton Business Expo-2022, and university grounds.

The students wore purpose-designed hoodies to promote the trials and to help identify them as trial ambassadors as part of the outreach work in the community, and created pop-up stands and a variety of information leaflets in different languages signposting people to the PRINCIPLE and PANORAMIC trials and how to access the study for those who may be eligible. All costs for developing information leaflets and promotional materials, including the hoodies, were kindly provided by the University of Bolton. The trials' Inclusion and Diversity Lead also engaged the local press.

Results

The initial community outreach work with PRINCIPLE received positive feedback from the target audience, indicating it was highly popular and informative. The success of this initiative gained further approval for the PANORAMIC trial to support recruitment, and for a second year a new cohort of students was recruited under a fresh 3-month initiative.

Discussion

Recruitment to clinical trials needs to be more inclusive and better representative of our diverse population. Effective and more targeted strategies with dedicated investment are vital. Utilising students in university towns and cities located in areas of high deprivation and densely populated ethnic minority communities are one way forward in improving

recruitment of underserved communities to clinical trials.

12.3. The Role of Language and Translation

The PANORAMIC study team developed accessible, culturally appropriate and user-friendly materials in eight different languages which were available on the study website. Additionally, patient information leaflets were developed in an 'easy read' format and available for sites and participants where this would be helpful. There was little dedicated funding for developing translation materials, information resources and videos for this study, and so translation services were kindly organised by the Inclusion and Diversity Lead and conducted by colleagues from the world Council of Hindus, World Tamil Organisation (UK), BAPIO, Muslim Doctors Cymru, BIMA, Agility Life Sciences, the British Indian Psychiatric Association (BIPA), Lincolnshire Partnership NHS Foundation Trust, and BAPS Temple Neasden.

12.4. Community Pharmacy

Community pharmacies were ideally located to reach out to underserved communities and people from diverse backgrounds as they are often situated within these communities, and have a high level of established trust and respect through the services they provide. As such, community pharmacies play an important part in supporting recruitment to clinical trials. Engagement was established and proved important throughout the delivery of the PANORAMIC study. Building on the learning from PRINCIPLE, pharmacies shared HRA-approved posters signposting patients to the decentralised PANORAMIC trial website.

The trial was also promoted through other pharmacy settings, and across the four nations in agreement with the DA NHS Chief Pharmaceutical Officers. Pharmacists from ethnic minority backgrounds also produced videos of the posters in different languages to be shared through their own organisations, and often through social media, to widen public awareness of the study. As well as raising the profile of the trial and encouraging recruitment, this was part of the EDI strategy employed by the trial team to improve research inclusion of participants in ethnically diverse and deprived communities.

The PANORAMIC team also engaged with the GPC who supported the trial by reaching out to its pharmacy registrants encouraging them to promote the trial, via its website and social media platforms and through its regular news information bulletin, '*Regulate*' (see Figure 11), sent to all pharmacy registrants opting in who had opted to receive the bulletin. This was the first time that a UK regulator of a healthcare profession had ever engaged and supported a clinical trial on this scale, and signalled their support in highlighting the importance of recruitment to clinical trials through close engagement with underserved communities. The impact of having pharmacy as the 'foot soldiers' in the community enabled the wider visibility of the trials in areas and communities not always reached before, and on a consistent basis across the UK for two national large-scale clinical trials.

In addition, pharmacy media should not be underestimated, and could be utilised more through greater collaboration and closer involvement to raise awareness and promote the importance of clinical trials. By boosting capacity and actively reaching out to engage underserved and more diverse communities through trusted channels such as these, research teams would be

better positioned to ensure that they better serve the healthcare needs of everyone more effectively across the UK.

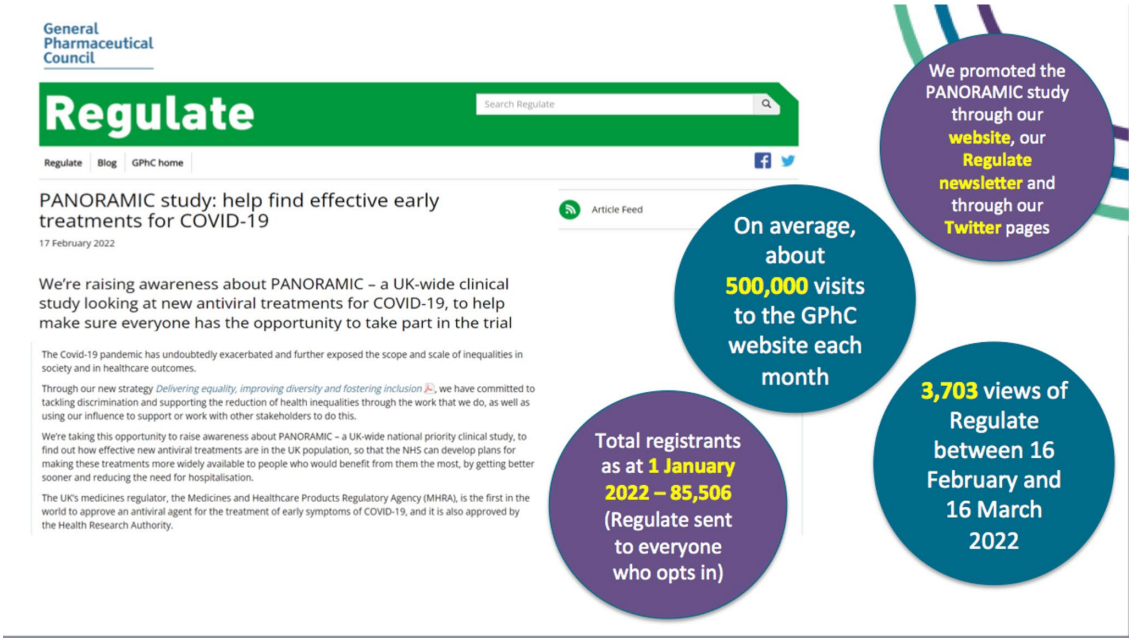

Figure 11. Screenshot from the General Pharmaceutical Council showing website traffic.

12.5. Evidence of Impact

Of the 26,411 participants randomised to the molnupiravir arm, 1,507 participants were from ethnic minority backgrounds: 800 Asian (3.2%), 153 Black (0.6%), 389 Mixed (1.6%), and 165 Other (0.7%), exceeding national census proportions for many key indices (Butler, et al., 2023).

12.6. Successes of the EDI Strategy

Extending and building on the earlier learnings from the PRINCIPLE platform, the EDI strategy used in PANORAMIC was innovative and groundbreaking in various ways, adding to the uniqueness of the platform trial and its infrastructure. The innovative and novel EDI methods employed maximised equity and research inclusion by providing an understanding of the complexity of ethnic and intersectional heterogeneity, and diversity of cultural beliefs, attitudes, and behaviours. Meanwhile, the use of the UK-wide pharmacy network (including its regulators and community pharmacies) played a vital role in reaching out to underserved communities and helping to raise the awareness of clinical trials in primary care and therefore help recruitment of underserved communities across different settings and geographies thereby supporting recruitment at scale.

The collaborative approach used with key stakeholders and organisations gave a sense of shared ownership of the directives, and participant diversity was further ensured through partnerships with national faith organisations. Places of worship, religious and community leaders from different religious and cultural backgrounds played a very helpful role in raising the awareness of clinical trials, and were crucial to ensuring that the evidence gathered was more representative of our diverse communities. Working with medical organisations, particularly organisations of ethnic minority origins, and with institutions across the four nations of the UK, also enabled sustainable engagement of people from ethnic minority populations, and from a very wide geographical area, in this research.

Lastly, student outreach initiatives through universities situated in areas of high deprivation and densely populated ethnic minorities promoted clinical research within communities and were a valuable resource. Engagement with Asian media channels and social media platforms further supported traditional communication methods to raise awareness of the trials by directly reaching out to underserved communities. The media routes used are outlined in Appendix 7. The sharing of the results of the study via the news, journals, international platforms of science and research, including through DHSC platforms, is expected to promote engagement with research in these communities moving forward.

12.7. Challenges of the EDI Strategy

Despite the success of the PANORAMIC EDI strategy in ensuring diversity in the participant population, there were clear challenges to the recruitment process, given the enormity of the task and the historic lack of engagement of participants from underserved communities with clinical trials. This included having to lean on repeated goodwill from community and faith-based organisations and their leaders, as well as pharmacy outlets for their new and continued support. There was no funding to support the outreach work, which included creating information resources and ensuring that translations in different languages were both culturally-sensitive and accurate, and so ensuring EDI engagement activities were sustainable, and that trust and relationships with communities who historically have a greater reluctance to engage with research, was a challenge.

Meanwhile, competing priorities and a lack of a sense of ownership over the study led to healthcare professionals across the landscape requiring reminders to promote the study, which may have been compounded by a lack of recognised methods for informing stakeholders of changes to study inclusion and exclusion criteria. Such communication blockers were also noted when seeking to ensure the final results of the trials were conveyed to the participants in an easily accessible and understood manner, another cornerstone of building trust within underserved communities and perpetuating a willingness to engage in research.

In order for meaningful community outreach work to have any success and longevity, it requires appropriate investment of both finances and time, effective communication channels, and ongoing relationships of trust, respect and confidence. These relationships must be established over time, and not be perceived as being transient or a one-off measure.

The influence of the pandemic was critical in building momentum in this space. Through the PRINCIPLE and PANORAMIC trials there has been continued work to build on and share learnings for the future through the newly established Centre for Research Equity at the University of Oxford.

13. Patient and Public Involvement (PPI)

PPI was embedded into the whole lifecycle of the PANORAMIC study, building on the contribution made to the design of the PRINCIPLE study. The study team established a central study PPI group composed of 7 participants and carers who had lived experience of COVID-19 infection themselves or within their families. This included participants with conditions in the clinically extremely vulnerable categories as defined by Government guidance, a participant and carer with learning disability, and participants from different ethnic backgrounds.

This group worked to support document and protocol development for this study, advise on evolving recruitment strategies and provide ongoing support regarding study amendments, study flow, and dissemination. They met weekly for an hour during the set-up phase of PANORAMIC, and quarterly thereafter. They reviewed patient-facing trial materials and advertisements, advised on patient flow through the study and supported the study team's work pioneering efficient processes to appropriately and ethically access patient data in order to achieve sufficient participants. They also informed and supported dissemination of results via the study website, social media, press releases and publications.

In addition to this central PPI support, additional PPI involvement was designed as outlined in the following sections of the report.

13.1. PPI input into Recruitment, Interpretation of Findings, and Dissemination

Since PANORAMIC needed to rapidly achieve high volumes of recruited participants, the team worked with a wide range of public contributors to ensure that the trial was promoted and accessible to the broadest possible range of participants. They continued to engage with these groups to ensure that the plans for dissemination were fit for purpose in all of the communities who have engaged with the trial. This included:

- UK four-nation PPI groups meeting prior to trial launch, during the study to optimise process, and to support dissemination, delivered by trial leads in each Devolved Administration.
- Focus meetings with ethnic and religious community leaders (see Section 12).
- Encouraging GP Hubs delivering more intense aspects of the study to discuss the study with Patient Participation Groups (PPGs) to obtain input on study processes.

13.2. PPI Input into Study Management and Oversight

Two members of the central study PPI group represented this group on the independent Trial Steering Committee (TSC) to oversee the progress of the study.

13.2.1. Successes

Rapid highly-engaged support from the central PPI group allowed the team to make crucial improvements to documents to ensure that participant flow through the study was as clearly signposted and as easy to navigate as possible. An 'easy read' PIS was developed, which was substantially edited by the PPI group, in particular by their public participant with a learning disability and their sister, who worked together to give very helpful feedback. By including contributors who considered how language and imagery would be interpreted by their ethnic communities, the team avoided using inappropriate terminology and ensured that study

materials were representative of all the communities they aimed to recruit, for example in the pictures included in the participant information.

13.2.2. Challenges

Despite the success of the PPI group in developing easy read patient information sheets (PIS), the pace of trial set-up meant that often important edits to documents suggested by the group had to be included in amendments rather than being made before document approval. This could be frustrating for the PPI contributors as they did not see their efforts turn into rapid changes in the trial. In addition, the 4 nation PPI groups were not particularly successful in suggesting or modifying plans for local systems which had to be addressed at much more technical levels, which PPI input could not have identified. Lastly, the complexity of the statistical approach meant that PPI members of the TSC sometimes struggled to fully engage. This was improved by having a specific slot for PPI discussion within the agenda and promoting the ability of these members to query terminology 'live' during the meeting using the chat function, however.

14. Workforce

As this was a priority study, the shared NIHR CRN workforce pivoted to support PANORAMIC, and the willingness and enthusiasm of staff throughout the UK to engage in this proved vital, with the success of PANORAMIC highlighting the importance and relevance of research to clinical practice. Strong leadership in this space paved the way for success and helped to maintain positivity throughout, while the study itself brought the workforce together from across specialities and disciplines, enabling great workforce development. However, by focusing on one study, support for others was necessarily reduced.

14.1. Collaborative Working

That strong collaboration between participating Hubs and Spokes, LCRNs, and the CTU team enabled flexible working in a joined-up, national approach is a key learning from the delivery of PANORAMIC. The ability of all organisations to redeploy staff as required, combined with regular meetings between organisations and building upon existing working relationships, supported a wide workforce mobilisation across traditional boundaries to provide a 'shared workforce' and allowed immediate cross-cover to account for workload fluctuations. While it is acknowledged that competing priorities and resource constraints led to instances in which timelines between workforces did not align and that an integrated workforce role embedded within the CTU would have supported broader workforce mobilisation, the ability to 'share' staff was felt to greatly support recruitment to this nationally important study.

Several models and governance structures were used throughout PANORAMIC to enable the workforce to transfer and share resources cross-organisationally. There were difficulties with different IT systems, processes, validation of skills and governance structures, and some of the solutions to these challenges should be embedded moving forward to allow quicker mobilisation in any future pandemic situation. For example, better ongoing governance structures created between sponsors and CTUs, a sponsorship strategy group, helped discuss sponsorship models that worked both for the sponsors and CTUs.

14.2. Workforce Planning

The tight timelines for the set-up and delivery of PANORAMIC made it difficult in some cases to plan the workforce appropriately. There were instances where staff were recruited but the study was not yet open to recruitment, and so these staff were lost to other roles. This was particularly difficult in the study's early stages when there were many unknown variables, but it became easier once the study was open to recruitment and could be monitored to facilitate adjustments (where needed).

14.3. Agile Workforce

Agile delivery teams were helpful to provide support, including cross-cover. However, not all regions were able to provide an equal Agile team workforce to Hubs and Spokes due to local staffing constraints, resulting in some participating practices feeling a greater degree of staffing pressure than others. Where additional staff members from outside the NIHR CRN or practice were sought (e.g. retired GPs), it was found that significant work was required to identify only a few additional members of staff, and that this support was fragmented, with staff offering only a few hours per week, whereas one full-time individual per region was preferred.

Consideration of how best to employ the support of the known workforce who were self-isolating during the pandemic would have been beneficial, e.g. managers having lists of staff that could be deployed would have identified this extra capacity in the system.

Figure 12. Example heat map of trainee GPs returning Expressions of Interest.

14.4. Increasing Workforce Capacity

Workforce capacity was addressed in a number of ways to ensure adequate staffing:

- **Shared workforce:** Mutual sharing of workforce between organisations. Collaborative working needs to be enabled moving forward, including redeployed staff.
- **Outside providers**: Agency and Livi (a private digital healthcare company) staff provided extra flexibility and resources within the CTU. This may have future potential, but service provision and research must be balanced to enable support for studies.
- **GP trainees:** Ten thousand trainee GPs were contacted around Christmas 2021 by the study team and the NIHR CRN team, but once they had declared their interest, problems were problems encountered about how they were employed, contracted and paid. While this did not benefit PANORAMIC directly, there exists an opportunity to up-skill this group and put processes in place to enable rapid mobilisation in future studies. To highlight potential workforce capacity to Hubs and Spokes where trainee GPs had completed expressions of interest about involvement, heat maps of the country were made (see Figure 12).
- **Returners to practice:** This represented a huge opportunity to improve workforce retention issues, and it was recognised that there were staff who are specifically attracted to this type of flexible remote-working. For PANORAMIC, it was essential that the expectation and ask were clear to support appropriate commitment.
- **Flexibility of delegated staff:** There were opportunities to look at the workforce more widely and support the development of capacity and capability, i.e. the opportunity for nurse PIs in the molnupiravir arm.

14.5. Associate Principal Investigator (PI) Scheme

The NIHR Associate PI scheme was also endorsed in the PANORAMIC study, and the use of the scheme proved highly successful and yielded significant long-term benefits. This initiative provided excellent opportunities for staff to enhance their skills and actively engage in research. In total, 15 Associate PIs were recruited to PANORAMIC throughout its duration.

14.6. Employment

The sheer volume of workforce needed to work at pace on this study was unprecedented and involved the whole system working together. This posed challenges when establishing the necessary employment agreements and checks for different staff groups from different settings, e.g. universities, NHS, primary care and agencies, and this created significant delays. To have oversight, the CTU, with the HRA, created a Standard Operative Procedure (SOP) to establish the 'right to work' on the study and ensure appropriate onboarding. For example an NHS to NHS agreement was not applicable as the CTU was a University department. Oxford University Teaching Hospital employees could have an honorary contract with the CTU, but LCRN staff outside of Oxford needed a letter of access.

Technical barriers to the use of the NHSD WebViewer were also observed initially as individuals using the tool required access to NHS Smartcards. While this issue was resolved for agency staff employed by the central study team to provide support, it limited the number of staff able to engage with the study at some practices, as roles across the GP system and roles recognised by the WebViewer did not always align (see Section 11 for further details).

14.7. Training, Skills and Experience

Another challenge associated with the volume of the workforce needed was gathering staff availability, and evidence of training and skills to support appropriate sign-off on the remote digital delegation log. One way to overcome this and assist the CTU was the 'NIHR CRN virtual research ward' and a repository of CVs and certificates collated by the NIHR CRN for this workforce to aid the CTU in onboarding (further information about the 'NIHR CRN virtual research ward' can be found in Case Study 7). This was further supported by the CTU and NIHR CRN devising a Standard Operating Procedure flowchart to streamline the process and included study-specific training declarations.

Rapid study-specific training was needed to support the workforce to deliver the trial. The CTU created a number of scripts and videos that were well received by staff, and learning packages were created for specific needs, i.e. a remote consent training which was initiated and has since been fully created on the NIHR Learn platform. Further training, e.g. cultural competence, would have helped reach underserved communities and increase inclusion in the trial. Alongside the learning resources, staff were supported in an online community, and 'NIHR CRN virtual research ward' staff received mentorship, which was valued by all staff.

14.8. Skilled Staff for Study Design and Set-Up

A workforce with specific skills, i.e. to set up databases, case report forms (CRFs) and activities that are required before you can open a trial, is important for a study of this scale. The infrastructure provided by publicly funded or academic CTUs was also essential. Robust design and set-up required many different skilled staff who were in short supply.

14.9. Four Nation Approach

Across the four nations, there were similar difficulties in validating people's skills and experience, workforce contracting, pay, and indemnity, and as such, a number of different employment mechanisms were used, including secondment, joint contracting and single-site employment. In Wales, a single all-Wales model was utilised that provided honorary contracts in single-NHS organisations and indemnified in this way. This was manageable here (and in Northern Ireland) due to the relatively small numbers of staff involved (10-15), though the small scale also created difficulty with the costs and relative resources needed to set-up the study (see Section 15 for further details).

14.10. Impact on Staff

Feedback obtained from staff working on PANORAMIC was very positive, and the innovative and collaborative working model was very well received. Staff reported that they felt valued for their contribution and that they received appropriate recognition to maintain their motivation and enthusiasm. Moreover, a staff survey of those involved in the 'NIHR CRN virtual research ward' provided positive feedback regarding the CTU buddy scheme induction and online group, but also reflected some of the aforementioned challenges with experience and adapting to the complexity of the trial. Clear expectations and communication with staff were important to prevent frustration, lack of understanding and delays. It was, however, observed that the scale and speed of the trial delivery took a toll on the publicly funded and academic clinical staff, due to the sustained and prolonged effort taken to ensure successful study delivery, impacting both the physical and mental health of some staff. This must be considered in future studies to prevent the attrition of skilled and experienced staff in both face-to-face and regulatory roles.

14.11. Ongoing Challenges

A sustainable workforce in the academic trials unit sector to set up and run priority trials is important, to work alongside and integrate with the NIHR CRN and NHS delivery. Baseline capacity, capability and preparedness are all essential to support future pandemic studies, and all have relevance to the delivery of other priority trials. Similarly, in light of the ever-changing pandemic response, a strong baseline of capable and skilled staff is important to support high-priority research alongside all other clinical studies, reinforcing that continual workforce training, upskilling and development opportunities are needed.

As it was difficult to predict workforce availability (along with ongoing challenges with workforce planning throughout), there was no resilience in the system on top of the rota cover to account for absence, fluctuating demand, additional unexpected tasks and changes, leading to increased burden on the staff in the system. There is now a huge expectation of how quickly projects can be turned around and the associated resources and mechanisms to support this. This needs to be carefully managed moving forward; and while the decentralised model employed by PANORAMIC was praised, the efficiency of this model did not necessarily mean fewer resources were required.

Case Study 7: The PANORAMIC 'NIHR CRN virtual research ward'

As central (CTU) recruitment to PANORAMIC increased, additional staffing was required to ensure participants self-referring to the CTU could be reviewed, consented, and recruited within required timeframes. The number of additional WTE staff required was around 30, which could not be provided by the Lead LCRN as normal research activity had resumed following the first wave of the pandemic. As this aspect of the study was remote, a decision was made to secure collective support from across the NIHR CRN to expedite delivery, with each LCRN allocating staff to support the CTU Team. The PANORAMIC 'NIHR CRN virtual research ward' was thereby set up to mobilise NIHR CRN staff from around the country to support central CTU recruitment to the PANORAMIC study.

A virtual ward is typically defined by NHS England as an environment "*allowing patients to get hospital-level care at home safely and in familiar surroundings, helping speed up their recovery while freeing up hospital beds for patients that need them most.*" However, for the purpose of the PANORAMIC study, the term 'NIHR CRN virtual research ward' meant "*a ring-fenced virtual environment of NIHR CRN staff to assist the CTU*".

It soon became clear that the onboarding and induction of these staff created a large volume of work for the CTU. Therefore, in support of the establishment of the 'NIHR CRN virtual research ward', an experienced NIHR CRN research nurse engaged with potential staff about the study, answered questions, established staff availability, and collected relevant delegation documentation. The NIHR CRN research nurse also initiated the CTU induction programme, ensuring necessary training was signed off, so the CTU could add volunteer staff to the delegation log and sign volunteers off to work. On an ongoing basis, the NIHR CRN provided the CTU with a daily rota of staff available to reduce the rostering burden.

Throughout this process, a number of issues were faced, including:

- Cross-organisational access to IT systems; individuals providing support to the CTU team did not have access to the required IT systems and so cross-organisational collaborative working was initially challenging.
- Identifying contractual requirements to allow onboarding of staff was initially challenging, leading to delays in identifying and recruiting volunteers.
- Staff selection by LCRNs required careful planning; as Agile team funding had just been increased at a local level, new starters were selected to support study recruitment but often found remote working difficult.
- The NIHR CRN project team was not embedded in the CTU so were not aware of all aspects required to provide the level of support needed by the CTU team.

As a result of the challenges encountered in establishing and delivering the 'NIHR CRN virtual research ward', a number of key learnings were identified. These included:

- IT system access must be ensured ahead of time to enable cross-organisational collaborative working under such agreements.
- Early HRA involvement with the provision of a clear SOP establishing the contractual requirements for different staff when working remotely is optimal, and will prevent delays in onboarding new members of staff.

- Being able to redeploy experienced research staff provides more experience to draw upon, and reduces stress on the workforce. Newly recruited Agile team colleagues may not be best placed in a virtual research ward environment.
- Having an NIHR CRN project lead embedded into the CTU further supports study delivery by ensuring that issues are noted and flagged as soon as they arise.
- CTU buddy systems and WhatsApp groups are invaluable to back up training when working remotely and provide colleagues with access to rapid expertise.
- After an initial introduction and period of establishing staff on rotas, staff respond well to self-rostering and enjoy the experience of remote working.

15. Devolved Administration Experience

15.1. Cross-UK Delivery of the Study

PANORAMIC was designed to be a four nation platform study allowing participants anywhere in the UK to take part in a national study. It was generally felt that this was achieved, although country-specific issues were encountered, including around both clinical delivery of COVID-19 treatments and differences in the delivery of primary care through different organisations in all four nations. Other issues encountered included problems around data sharing, particularly in Scotland, where a different legal basis for data and information exchange exists, and differences across the four nations in the study documentation, e.g. wording referring to NHSD in England was not appropriate in DAs. This needs to be considered for future trials at an early stage, to ensure that the PIS and study documentation are appropriate for use across the UK, avoiding the need for amendments.

There was however a willingness throughout the study to work collaboratively to successfully deliver the study, and close working with DA colleagues was very beneficial in resolving these issues and was considered to be a very positive experience. Initially there were weekly meetings to share best practice and innovation between countries. Significant changes to the delivery were taken forward at different times by different nations, yet a coordinated common communication strategy, prompted by regular meetings of all four nations, led to a joined-up approach to communication about the study. Communication examples include the excellent messaging from the Welsh Government to COVID-19 positive cases in Wales (see Figure 13).

Learnings from the pandemic included the navigation of local health delivery models, i.e. wider understanding of how studies could be delivered across all four nations, and this was further developed during the delivery of PANORAMIC. This understanding greatly aided the visibility of the systems and identified UK-wide challenges.

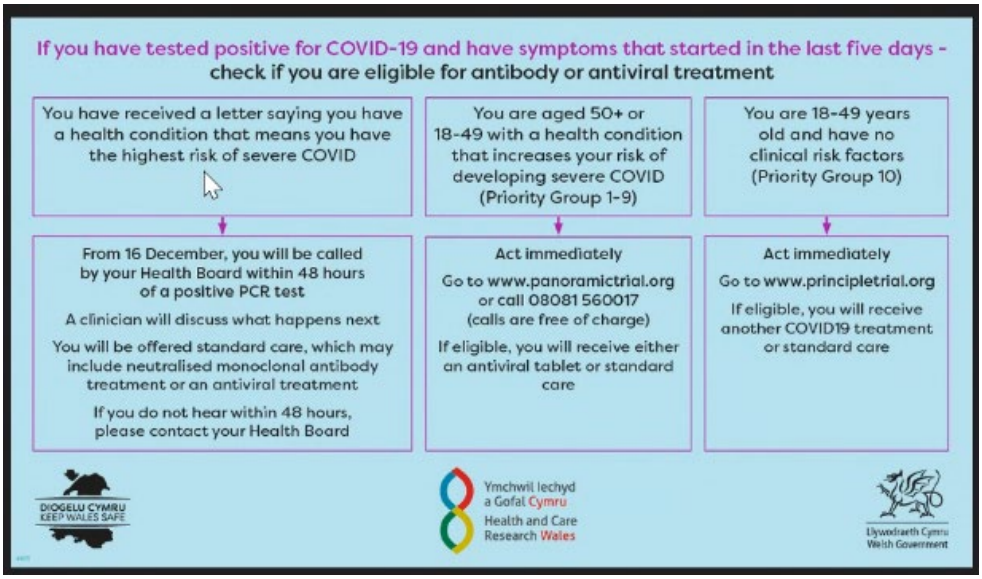

Figure 13. An example of communication from the Welsh Government to patients testing positive in Wales, highlighting both the PRINCIPLE and PANORAMIC studies.

The specific experiences of each of the three DAs are as follows:

15.2. Scotland

In Scotland, the PANORAMIC trial was delivered through Hubs established in Scottish Health Boards, as these centres have greater capacity than primary care to support clinical trials in Scotland. NHS Fife, Lothian, Highland and Grampian (covering a total of about 40% of the Scottish population) participated in the molnupiravir arm and NHS Lothian, Grampian, and Greater Glasgow & Clyde (covering about 50% of the Scottish population) participated in the Paxlovid arm. Other Health Boards were unable to participate due to a lack of capacity to take on this trial in addition to the other studies being supported.

15.2.1. Approvals and Set-Up Process

Delivery was coordinated by the NHS Research Scotland (NRS) Central Management Team (CMT) through initially weekly delivery calls that included trial teams in Scotland, the University of Oxford central trial team and others. Differences in the trial delivery model employed in Scotland and the rest of the UK (secondary compared with primary care), identifying sufficient trial delivery capacity given other competing COVID-19 related studies, and resolution of IG issues delayed the start. Approvals and amendments were fast tracked by Health Board R&D departments, but differing IG concerns across Health Boards were more challenging to address in an expedited manner. How these might be managed more efficiently is being addressed by a national working group that has been established by the NRS CMT.

Recruitment was supported in Scotland through the following means:

- Patients registering on the PANORAMIC central site were flagged to the relevant Hub based on their postcode. The Hubs had access to daily lists of positive COVID-19 LFT reports provided by Public Health Scotland (PHS), and were then pre-screened for eligible age groups.
- Electronic communications sent by the NHS Scotland T&P system following a positive LFT report directed patients to COVID-19 studies on a specially established NRS microsite which advertised and offered opportunities to participate in COVID-19 studies.
- Potentially vulnerable patients not eligible to receive antiviral medications directly were consented by the care team for contact by the research team about participation in PANORAMIC.
- The NHS Inform website directed patients to the study.
- Press notices and social media.

15.2.2. Study Delivery

Research nurses undertook eligibility checks and consented patients to the molnupiravir arm. For the Paxlovid arm the availability of the medical cover needed to consent was more limiting and initially there were issues to resolve around medical record data availability to trial teams to undertake the eligibility and safety checks needed. The other three home nations had the research infrastructure in primary care (for e.g. GCP trained GP practices with previous trial experience) so they could deploy a hub and spoke model for more effective recruitment.

15.2.3. Central Trial Management

- Scottish Hubs had good communications link up with the central site, with a dedicated contact in the trial team and weekly Scottish and four nation meetings. The central

prescribing and IMP couriered to patients worked well. Payments for the Paxlovid were considered inadequate as the screening process was time consuming, required a clinician and Scottish sites had to undertake additional safety calls at days 2 and 10 (managed by the central team for English sites).

- For both molnupiravir and Paxlovid arms, the central trial team in Oxford had the ability and permissions to review primary care records for any consenting patient across England. A similar central recruitment model was also set up in Wales and managed by PHW. This model was not feasible in Scotland as there was no facility or infrastructure to review patient notes centrally in Scotland. Consequently, the recruitment capacity in Scotland was reduced. A central model would have facilitated faster and more representative recruitment as pooled resources would have enabled some of the smaller health boards (see earlier point) to participate.

15.2.4. Outcome Data

Following application to the Public Benefit and Privacy Panel, approval to access Scottish outcome data (hospital admissions and deaths) was granted and these data were provided by the PHS electronic Data Research & Innovation Service (eDRIS) to support analyses.

15.2.5. Legacy Effects of PANORAMIC in Scotland

While Scotland was able to contribute to PANORAMIC there were a number of challenges to overcome and adaptations required. These are forming the basis of a review for improvements to support delivery of similar types of trials in the future. NHS IT system developments set out in the Scottish Government's Data Strategy for Health & Social Care could support data-enabled recruitment to similar trials in the future (Scottish Government, 2023).

15.3. Northern Ireland

The Primary Care Group of the Northern Ireland Clinical Research Network (NICRN) undertook Northern Ireland's participation in the PANORAMIC study. Initially two GPs with CTIMP clinical trial experience worked alongside the NICRN team and an academic GP trainee who took up a research fellowship to work exclusively on PANORAMIC in Northern Ireland, which was funded by the Northern Ireland Public Health Agency's Research and Development (PHA R&D). The delivery model was initially set up as a GP practice Hub and Spoke model, and then developed into a central recruitment model.

The initial Hub and Spoke model had two Hub GP practices receiving referrals electronically from neighbouring GP practices. Recruitment via this route was initially low since Northern Ireland GPs, unlike the rest of the UK, were not automatically electronically informed of positive COVID-19 cases in their patient lists. Significant work was then undertaken between NICRN and Digital Health and Care Northern Ireland (DHCNI), which resulted in two daily emails to the Hub practices with their positive cases listed. This approach resulted in a handful of participants for molnupiravir from each GP practice that acted as a recruitment Hub.

The second, more successful delivery model for molnupiravir used a similar model to Wales; the NICRN became a central Hub for recruitment. Through working with colleagues in DHCNI, a line about PANORAMIC was added to the automated track and trace text messages. Alongside mass public access to testing, this was undoubtedly a large reason for the success.

The use of a central registration process helped coordinate communication to the public as well as allowing the NICRN Primary Care Group to recruit, enrol and follow up all Northern Irish participants, without adding strain or workload to GP colleagues. This allowed everyone in Northern Ireland to be equally eligible to participate, regardless of geographical location. Participants were recruited from 79% (253/319) of Northern Ireland's GP practices, without adding to the workload of these practices. The demand to participate was unprecedented and in spring of 2022, up to 40 people a day were enrolled.

The second arm of the study, Paxlovid, provided more challenges. Two different delivery models were used - firstly, and most successfully, a central recruitment model, with sessional GPs checking eligibility due to the study protocol recruitments. Medical cover was provided, via GPs, Monday to Friday, with NICRN nursing colleagues following up participants. This was funded by PHA R&D until April 2023, when low incidence of COVID-19 and low study registrations made it possible for eligibility checking to be covered by the research fellow until the end of post in July 2023. The second delivery model for the Paxlovid arm invited all GP trainees across Northern Ireland to be part of the study and act as recruitment Hubs for their practices. Unfortunately, this method did not achieve the desired traction, likely due to the mounting pressure on general practice at the time.

Overall, the greatest successes of the Northern Ireland delivery model were linked to the greatest hurdles. Firstly, the automated text service facilitated the successful recruitment in both arms of the study. Secondly, due to the speed and clinical priority of the trial rollout, as well as being a pioneering four nation UK study, challenges emerged around data linkage and participant follow-up. The need for differences in wording for the different systems in each Devolved Administration also led to significant challenges. However, through collaborating with colleagues in the Department of Health, the Public Health Agency, the individual Health and Social Care (HSC) trusts and Business Services Organisation (BSO), data linkage was obtained for the first time in a study of this kind.

Whilst the research structures and digital health data systems in Northern Ireland are not as well established as in other parts of the UK, the NICRN team, alongside supportive colleagues at the University of Oxford, overcame many barriers. The challenge is to continue building on the developments and successes of PANORAMIC in Northern Ireland. The Northern Ireland PANORAMIC team demonstrated that the use of centrally recruiting models can generate great results, whilst protecting the workload and pressure on frontline General Practice.

15.4. Wales

Like England, Wales approached the PANORAMIC study with the intention of establishing a centralised recruitment model alongside Hubs and Spokes; however, learnings from the preceding PRINCIPLE trial showed that this was quite difficult, and did not result in strong nationwide engagement. As molnupiravir did not require enhanced patient safety monitoring, Wales employed a single centralised recruitment model operating from a one-nation hub. This decision also factored in the limited capacity of primary care services in Wales to deliver research, and led to Health and Care Research Wales, in partnership with Cardiff University, investigating options to shift the delivery model and take activity out of primary care.

While initially complex, remote recruitment using a medical rota was highly successful. Patients were alerted to the PANORAMIC study via public campaigns, or by SMS text message from the booking team, who would receive care lists directly from the source, review these, and make contact with potentially eligible individuals. This team approached this exercise by contacting those due to become ineligible for participation first, sending acknowledgement and holding emails to maintain engagement, and thanking those who were ineligible for their interest. Such expectation management resulted in a positive response from potential participants, and the enrollment of over 1,600 patients in Wales to the molnupiravir arm of the study. Though the Hub and Spoke model was revisited for the Paxlovid arm, expedited access for the central team to summary care records allowed activity to continue unimpeded. Follow-up was then undertaken by a clinical and administrative team in Cardiff University facilitated by the leadership role of a national PI, which bridged across both the NHS and Higher Education Institution (HEI). This team was initiated utilising existing GP academic fellows and then extended to include research nurses.

This model was not without its challenges, however. The rostering of clinicians was initially successful, but there were limits to the numbers of honorary contracts that would be awarded and questions were raised around cross-organisational indemnity. Ultimately, approximately 12 medics were given honorary contracts, though it proved challenging to manage large numbers of participants with such a lean team, especially as Wales did not take up the option of nurse-led screening due to the additional challenges this would bring. Building on existing HEI staff for follow-up, such as GP academic fellows, allowed the honorary contract staff to focus on recruitment. Ready access to relevant teams and people were felt to be key to ensuring this model worked, with the national PI and scientific lead always available by phone and regularly holding meetings and training sessions, thereby ensuring engagement across the country.

"It is easy to underestimate the intensity of the activity required in decentralised models. You have to work hard at keeping communication effective" - National Head of Research Delivery Nurses, Midwives and Allied Health Professionals, Health and Care Research Wales.

As a DA, the Wales team felt fortunate to have both scientific and operational input into protocol development and a direct line to local government. This led to options in delivery models, and an opportunity to shape the study to adapt to local operating systems and nationally appropriate wording. The relative simplicity of the protocol was hugely beneficial and allowed the centralised model to be stood up quickly, while its adaptability - such as the rapid removal for confirmed COVID-19 infection in response to the Government withdrawal of free testing - streamlined activities across the UK. The ability to manage drugs centrally was also felt to provide numerous opportunities and be repeatable, and was outlined as a consideration for future studies as this would allow more studies to be run in a similar way.

In all, while capacity in Wales was not high, engagement was, and a lot of interest was shown by GPs who would not usually be involved in research. The Welsh primary care environment, while stretched, is very keen and willing to participate in similar studies in future.

16. References

Bower, P., Grigoroglou, C., Anselmi, L., Kontopantelis, E., Sutton, M., Ashworth, M., Evans, P., Lock, S., Smye, S., Abel, K. (2020). Is health research undertaken where the burden of disease is greatest? Observational study of geographical inequalities in recruitment to research in England 2013-2018. *BMC Med*. 18(1):133.

Butler, C.C., Hobbs, F.D.R., Gbinigie, O.A., Rahman, N.M., Hayward, G., Richards, D.B., Dorward, J., Lowe, D.M., Standing, J.F., Breuer, J., Khoo, S., Petrou, S., Hood, K., Nguyen-Van-Tam, J.S., Patel, M.G., Saville, B.R., Marion, J., Ogburn, E., Allen, J., Rutter, H., Francis, N., Thomas, N.P.B., Evans, P., Dobson, M., Madden, T.A., Holmes, J., Harris, V., Png, M.E., Lown, M., van Hecke, O., Detry, M.A., Saunders, C.T., Fitzgerald, M., Berry, N.S., Mwandigha, L., Galal, U., Mort, S., Jani, B.D., Hart, N.D., Ahmed, H., Butler, D., McKenna, M., Chalk, J., Lavallee, L., Hadley, E., Cureton, L., Benysek, M., Andersson, M., Coates, M., Barrett, S., Bateman, C., Davies, J.C., Raymundo -Wood, I., Ustianowski, A., Carson-Stevens, A., Yu, L.M., Little, P. PANORAMIC Trial Collaborative Group (2023). Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. *Lancet*. 401(10373):281-293.

Butler, C.C., Yu, L.M., Dorward, J., Gbinigie, O., Hayward, G., Saville, B.R., Van Hecke, O., Berry, N., Detry, M.A., Saunders, C., Fitzgerald, M., Harris, V., Djukanovic, R., Gadola, S., Kirkpatrick, J., de Lusignan, S., Ogburn, E., Evans, P.H., Thomas, N.P.B., Patel, M.G., Hobbs, F.D.R., PRINCIPLE Trial Collaborative Group (2021). Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet Respir Med*. 9(9):1010-1020.

Dawson, S., Banister, K., Biggs, K., Cotton, S., Devane, D., Gardner, H., Gillies, K., Gopalakrishnan, G., Isaacs, T., Khunti, K., Nichol, A., Parker, A., Russell, A.M., Shepherd, V., Shiely, F., Shorter, G., Starling, B., Williams, H., Willis, A., Witham, M.D., Treweek, S. (2022). Trial Forge Guidance 3: randomised trials and how to recruit and retain individuals from ethnic minority groups-practical guidance to support better practice. *Trials*, *23*(1), 672.

Department of Health and Social Care, The Executive Office (Northern Ireland), The Scottish Government, and Welsh Government. (2021). The Future of UK Clinical Research Delivery. [online] Available at: https://www.gov.uk/government /publications/the-future-of-uk-clinical-research-delivery. [Accessed 15 March 2024].

Dorward, J., Yu, L.M., Hayward, G., Saville, B.R., Gbinigie, O., Van Hecke, O., Ogburn, E., Evans, P.H., Thomas, N.P., Patel, M.G., Richards, D., Berry, N., Detry, M.A., Saunders, C., Fitzgerald, M., Harris, V., Shanyinde, M., de Lusignan, S., Andersson, M.I., Butler, C.C., Hobbs, F.R.; PRINCIPLE Trial Collaborative Group (2022). Colchicine for COVID-19 in the community (PRINCIPLE): a randomised, controlled, adaptive platform trial. *Br J Gen Pract*. 72(720):e446-e455.

Gahagan, J., Gray, K., Whynacht, A. (2015). Sex and gender matter in health research: addressing health inequities in health research reporting. *Int J Equity Health* 14, 12.

Gbinigie, O., Ogburn, E., Allen, J., Dorward, J., Dobson, M., Madden, T.A., Yu, L.M., Lowe, D.M., Rahman, N., Petrou, S., Richards, D., Hood, K., Patel, M., Saville, B.R., Marion, J., Holmes, J., Png, M.E., Hayward, G., Lown, M., Harris, V., Jani, B., Hart, N., Khoo, S., Rutter, H., Chalk, J., Standing, J.F., Breuer, J., Lavallee, L., Hadley, E., Cureton, L., Benysek, M., Andersson, M.I., Francis, N., Thomas, N.P.B., Evans, P., van Hecke,

O., Koshkouei, M., Coates, M., Barrett, S., Bateman, C., Davies, J., Raymundo-Wood, I., Ustianowski, A., Nguyen-Van-Tam, J., Carson-Stevens, A., Hobbs, R., Little, P., Butler, C.C. (2023). Platform adaptive trial of novel antivirals for early treatment of COVID-19 In the community (PANORAMIC): protocol for a randomised, controlled, open-label, adaptive platform trial of community novel antiviral treatment of COVID-19 in people at increased risk of more severe disease. *BMJ Open*. 13(8):e069176.

Goodwin, V.A., Low, M.S.A., Quinn, T.J., Cockcroft, E.J., Shepherd, V., Evans, P.H., Henderson, E.J., Mahmood, F., Ni Lochlainn, M., Needham, C., Underwood, B.R., Arora, A., Witham, M.D. (2023). Including older people in health and social care research: best practice recommendations based on the INCLUDE framework. *Age and Ageing*. *52(6)*:afad082.

Hayward, G., Butler, C.C., Yu, L.M., Saville, B.R., Berry, N., Dorward, J., Gbinigie, O., van Hecke, O., Ogburn, E., Swayze, H., Bongard, E., Allen, J., Tonner, S., Rutter, H., Tonkin-Crine, S., Borek, A., Judge, D., Grabey, J., de Lusignan, S., Thomas, N.P.B., Evans, P.H., Andersson, M.I., Llewelyn, M., Patel, M., Hopkins, S., Hobbs, F.D.R. (2021). Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE): protocol for a randomised, controlled, open-label, adaptive platform, trial of community treatment of COVID-19 syndromic illness in people at higher risk. *BMJ Open*. 11(6):e046799.

Hayward, G., Yu, L.M., Little, P., Gbinigie, O., Shanyinde, M., Harris, V., Dorward, J., Saville, B.R., Berry, N., Evans, P.H., Thomas, N.P.B., Patel, M.G., Richards, D., Hecke, O.V., Detry, M.A., Saunders, C., Fitzgerald, M., Robinson, J., Latimer-Bell, C., Allen, J., Ogburn, E., Grabey, J., de Lusignan, S., Hobbs, F.R., Butler, C.C.; PRINCIPLE Trial Collaborative Group. (2024). Ivermectin for COVID-19 in adults in the community (PRINCIPLE): An open, randomised, controlled, adaptive platform trial of short- and longer-term outcomes. *J Infect*. 88(4):106130.

Healthtalk (DIPEx). (2022). Difficulties and barriers to involvement. [online] Available at: https://healthtalk.org/experiences/patient-and-public-involvement-research/difficulties-and-barriers-to-involvement/ [Accessed 13 March 2024].

HRA, CRN, and R&D Forum. 2023. Information Governance Information for Organisations Participating in Research Studies – Joint Statement. [online]. Available at: https://rdforum.nhs.uk/wp-content/uploads/2023/08/Joint-IG-awareness-statement-HRA-CRN-RDF-final-August-2023.pdf. [Accessed 04 June 2024].

International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC). (2020). COVID-19 Report: 27 April 2020. [online] Available at: https://media.tghn.org/medialibrary/2020/05/ISARIC_Data_Platform_COVID-19_Report_27APR20.pdf [Accessed 12 March 2024].

Kadambari, S., Vanderslott, S. (2021). Lessons about COVID-19 vaccine hesitancy among minority ethnic people in the UK. *The Lancet. Infectious diseases*, *21*(9), 1204–1206.

Kapadia, D., Zhang, J., Salway, S., Nazroo, J., Booth, A., Villarroel-Williams, N., Becares, L., Esmail, A. (2022). Ethnic Inequalities in Healthcare: A Rapid Evidence Review. NHS Race & Health Observatory. [online] Available at: https://www.nhsrho.org/wp-content/uploads/2023/05/RHO-Rapid-Review-Final-Report_.pdf [Accessed 12 March 2024].

Khunti, K., Singh, A.K., Pareek, M., Hanif, W. (2020) Is ethnicity linked to incidence or outcomes of covid-19? *BMJ*. 369:m1548.

Masoli, J.A.H., Down, K., Nestor, G., Hudson, S., O'Brien, J.T., Williamson, J.D., Young, C.A., Carroll, C. (2021). NIHR Remote Trial Delivery Working Group. A report from the NIHR UK working group on remote trial delivery for the COVID-19 pandemic and beyond. *Trials*. 22(1):911.

Mitchell, E.J., Appelbe, D., Bravery, A., Culliford, L., Evans, H., Farrin, A.J., Gillies, K., Hood, K., Love, S.B., Sydes, M.R., Williamson, P.R., Wakefield, N.; as part of the e-Consent collaborative group. (2023) e-Consent in UK academic-led clinical trials: current practice, challenges and the need for more evidence. *Trials*. 24(1):657.

Murali, M., Gumber, L., Jethwa, H., Ganesh, D., Hartmann-Boyce, J., Sood, H., Zaccardi, F., Khunti, K. (2023) Ethnic minority representation in UK COVID-19 trials: systematic review and meta-analysis. *BMC Med. 21*(1):111.

NIHR. (2020). Improving inclusion of under-served groups in clinical research: Guidance from INCLUDE project. [online] Available at: https://www.nihr.ac.uk/documents/improving-inclusion-of-under-served-groups-in-clinical-research-guidance-from-include-project/25435 [Accessed 12 March 2024].

Png, M.E., Harris, V., Grabey, J., Hart, N.D., Jani, B.D., Butler, D., Carson-Stevens, A., Coates, M., Cureton, L., Dobson, M., Dorward, J., Evans, P., Francis, N., Gbinigie, O.A., Hayward, G., Holmes, J., Hood, K., Khoo, S., Ahmed, H., Lown, M., Mckenna, M., Mort, S., Nguyen-Van-Tam, J., Rahman, N., Richards, D.B., Thomas, N., van Hecke, O., Hobbs, F.R., Little, P., Yu, L.M., Butler, C.C., Petrou, S. (2024). Cost-utility analysis of molnupiravir plus usual care versus usual care alone as early treatment for community-based adults with COVID-19 and increased risk of adverse outcomes in the UK PANORAMIC trial. *Br J Gen Pract*. 16:BJGP.2023.0444.

Powell, R.A., Njoku, C., Elangovan, R., Sathyamoorthy, G., Ocloo, J., Thayil, S., Rao, M. (2022). Tackling racism in UK health research. *BMJ (Clinical research ed.)*, 376, e065574.

PRINCIPLE Trial Collaborative Group (2021). Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 397(10279) :1063-1074.

Public Health England. (2020). Beyond the Data: Understanding the impact of COVID-19 on BAME groups. [online] Available at: https://assets.publishing.service.gov.uk/media/5ee761fce90e070435f5a9dd/COVID_stakeholder_engagement_synthesis_beyond_the_data.pdf [Accessed 12 March 2024].

Redwood, S., Gill, P.S. (2013). Under-representation of minority ethnic groups in research--call for action. *Br J Gen Pract*. 63(612):342-3.

Saville, B.R., Berry, SM. (2016). Efficiencies of platform clinical trials: A vision of the future. Clin *Trials*. 13(3):358-66.

Scottish Government (2023). Health and Social Care: Data Strategy [online]. Available at: https://assets.publishing.service.gov.uk/media/5ee761fce90e070435f5a9dd/COVID_stakeholder_engagement_synthesis_beyond_the_data.pdf [Accessed 21 May 2024].

Skea, Z.C., Newlands, R., Gillies, K. (2019). Exploring non-retention in clinical trials: a meta-ethnographic synthesis of studies reporting participant reasons for drop out. *BMJ Open*, 9(6), e021959.

Standing, J.F., Buggiotti, L., Guerra-Assuncao, J.A., Woodall, M., Ellis, S., Agyeman, A.A., Miller, C., Okechukwu, M., Kirkpatrick, E., Jacobs, A.I., Williams, C.A., Roy, S., Martin-Bernal, L.M., Williams, R., Smith, C.M., Sanderson, T., Ashford, F.B., Emmanuel, B., Afzal, Z.M., Shields, A., Richter, A.G., Dorward, J., Gbinigie, O., Van Hecke, O., Lown, M., Francis, N., Jani, B., Richards, D.B., Rahman, N.M., Yu, L.M., Thomas, N.P.B., Hart, N.D., Evans, P., Andersson, M., Hayward, G., Hood, K., Nguyen-Van-Tam, J.S., Little, P., Hobbs, F.D.R., Khoo, S., Butler, C., Lowe, D.M., Breuer, J.; PANORAMIC Virology Group. (2024). Randomized controlled trial of molnupiravir SARS-CoV-2 viral and antibody response in at-risk adult outpatients. *Nat Commun.* 15(1):1652.

Tonner, E., Crawshaw, S., Dolman, M., Chambers, E., Williamson, J., Thomas, N., Hobbs, R., Little, P., Butler, C., Evans, P. (2023). Innovative methods of recruitment through the NIHR Clinical Research Network (CRN) into large-scale pandemic trials in primary care: the PANORAMIC trial experience. *BJGP*. 73 (suppl 1): bjgp23X733665.

Treweek, S., Forouhi, N.G., Narayan, K.M.V., Khunti, K. (2020). COVID-19 and ethnicity: who will research results apply to? *Lancet*. 395(10242):1955-1957.

Wafa, H., Lee, C.N., Desai, R., Jackson, T.L., Wang, Y. (2023). THE COMPLIANCE PLOT: A novel bespoke approach to monitor and examine protocol-adherence in clinical trials. In *6th International Clinical Trials Methodology Conference, 3rd – 6th October 2022, Harrogate, UK, Book of Abstracts* (pp. 72-72). [PS3B-03]

Watkinson, R.E., Sutton, M., Turner, A.J. (2021). Ethnic inequalities in health-related quality of life among older adults in England: secondary analysis of a national cross-sectional survey. *Lancet*. 6(3):E145-E154.

Wilkinson, E. (2023). Ethnicity research gap: is pharmacy the key to making trials more representative? [online] *The Pharmaceutical Journal*. Available at: https://pharmaceutical-journal.com/article/feature/ethnicity-research-gap-is-pharmacy-the-key-to-making-trials-more-representative [Accessed 13 March 2024].

Williamson, E.J., Walker, A.J., Bhaskaran, K., Bacon, S., Bates, C., Morton, C.E., Curtis, H.J., Mehrkar, A., Evans, D., Inglesby, P., Cockburn, J., McDonald, H.I., MacKenna, B., Tomlinson, L., Douglas, I.J., Rentsch, C.T., Mathur, R., Wong, A.Y.S., Grieve, R., Harrison, D., Forbes, H., Schultze, A., Croker, R., Parry, J., Hester, F., Harper, S., Perera, R., Evans, S.J.W., Smeeth, L., Goldacre, B. (2020) Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 584(7821):430-436.

Witham, M.D., Anderson, E., Carroll, C., Dark, P.M., Down, K., Hall, A.S., Knee, J., Maier, R.H., Mountain, G.A., Nestor, G., Oliva, L., Prowse, S.R., Tortice, A., Wason, J., Rochester, L., INCLUDE writing group. (2020). Developing a roadmap to improve trial delivery for under-served groups: results from a UK multi-stakeholder process. *Trials*. 21(1):694.

Yu, L.M., Bafadhel, M., Dorward, J., Hayward, G., Saville, B.R., Gbinigie, O., Van Hecke, O., Ogburn, E., Evans, P.H., Thomas, N.P.B., Patel, M.G., Richards, D., Berry, N., Detry, M.A., Saunders, C., Fitzgerald, M., Harris, V., Shanyinde, M., de Lusignan, S., Andersson, M.I., Barnes, P.J., Russell, R.E.K., Nicolau, D.V. Jr., Ramakrishnan, S., Hobbs, F.D.R., Butler, C.C. PRINCIPLE Trial Collaborative Group (2021). Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK

(PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 398(10303):843-855. Erratum in: Lancet. 2021 Aug 18.

17. Appendices

Appendix 1. Contributors to the Report, and Workshop Attendees.

The following individuals and stakeholders contributed to the collation of this report.

Contributors

- **Wales**

Professor Kerry Hood: Professor of Trials and Director of the Centre for Trials Research, College of Biomedical and Life Sciences, Cardiff University.
Professor Andrew Carson-Stevens: Principal Investigator for Wales, and Professor of Patient Safety, Division of Population Medicine, Cardiff University.
Jayne Goodwin: National Head of Research Delivery Nurses, Midwives and Allied Health Professionals, Health and Care Research Wales.
Dr Yvette Ellis: National Head of Research Delivery Operations, Health and Care Research Wales.

- **Northern Ireland**

Dr Daniel Butler: GP Research Fellow.
Professor Nigel Hart: Principal Investigator for Northern Ireland, and Associate Director for General Practice and Primary Care, Centre for Medical Education, Queen's University Belfast.

- **Scotland**

Dr Ellen Drost: Primary Care Network Manager, NHS Research Scotland.
Dr Bhautesh Jani: Principal Investigator for Scotland, and Co-Primary Care Research Champion, NHS Research Scotland.
Dr Stephen Kelly: Science Manager, NHS Research Scotland Central Management Team.
Dr Tom Barlow: Senior Research Manager, Chief Scientist Office for Scotland.

- **Cumbria**

Dr Stacey Fisher: Research GP, North Cumbria Integrated Care.
Hilary Allan: Research Delivery Manager, CRNNorth East and North Cumbria.

- **Manchester**

Danielle Wilcock: Assistant Research Delivery Manager, CRNGreater Manchester.

- **OneNorwich**

Rachel Stebbings: Clinical Studies Research Nurse, ARC East of England.
Kate McCloskey: Lead Community and Care Manager, CRNEast of England.
Helen Jung: Lead Primary Care Manager, CRN East of England.
Karen Tibbenham: Research Delivery Manager, CRNEast of England.

- **Lancaster**

Lee Bullen: Senior Research Nurse, CRNNorth West Coast.

- **Others**

Professor Mahendra Patel: Inclusivity and Diversity Lead, Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences, University of Oxford.
Professor Gail Hayward: Associate Professor of Primary Care and Director of the NIHR Community Healthcare MIC, Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences, University of Oxford, University of Oxford.
Nancy Hopewell: Workforce Development Lead, GCP Programme Lead, Joint Chief Nurse and Joint Head of Research Workforce, CRNThames Valley and South Midlands.
Philip Milne: Senior Project Manager, NIHR CRN Coordinating Centre.
Professor David Lowe: Consultant Immunologist, Royal Free London NHS Foundation Trust and Principal Investigator, Institute of Immunity and Transplantation, University College London.

Workshop Attendees

Mark Ainsworth: Business Analyst, NIHR CRN Coordinating Centre.
Dr Julie Allen: Senior Clinical Trial Manager, Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences, University of Oxford.
Paul Biagioni: Northern Ireland Clinical Research Network Senior Manager, NICRN Coordinating Centre.
Professor Chris Butler: Professor of Primary Care, Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences, University of Oxford.
Dr Emma Chambers: Research Delivery Lead, NIHR CRN Coordinating Centre.
Ferdousi Chowdhury: Assistant Director, Research Governance Ethics and Assurance, University of Oxford.
Vicki Clatworthy: Study Support Service Facilitator, CRNThames Valley and South Midlands.
Dr Sarah Crawshaw: Head of Research Delivery, NIHR CRN Coordinating Centre.
Lucy Cureton: Senior Clinical Trial Manager,Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences, University of Oxford.
Dr Mark Dolman: Deputy Chief Operating Officer, CRNThames Valley and South Midlands.
Dr Ellen Drost: Primary Care Network Manager, NHS Research Scotland.
Mark Evans: Research Data and Digital Transformation Manager, CRNWest Midlands.
Professor Philip Evans: Deputy Medical Director, NIHR CRN Coordinating Centre.
Kate Fenton: Senior Research Manager, NIHR Evaluation, Trials and Studies Coordinating Centre.
Dr Lisa Gibbons - General Practitioner, Rolle Medical Partnership, Exmouth. Primary Care Lead, NIHR CRN South West Peninsula. Co-Chair Primary Care Strategy Digital Sub Group, NIHR Clinical Research Network Coordinating Centre
Jayne Goodwin: National Head of Research Delivery Nurses, Midwives and Allied Health Professionals, Health and Care Research Wales.
Professor Richard Hobbs: Nuffield Professor of Primary Care Health Sciences, Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences, University of Oxford
Nancy Hopewell: Joint Head of Research Workforce, CRNThames Valley and South Midlands.
Professor Nick Lemoine: Medical Director, NIHR CRN Coordinating Centre.
Fran Lister: Communications Manager, NIHR CRN Coordinating Centre.
Kathryn Lucas: Study Support Service Manager, CRNThames Valley and South Midlands.
Philip Milne: Senior Project Manager, NIHR CRN Coordinating Centre.

Marjia Monsur: Head of Research Strategy and Delivery, Antivirals Taskforce, Department of Health and Social Care.
Dafni Moschidou: Senior Policy Manager, Department of Health and Social Care.
Alistair Nicholson: Head of Coordination and Standardisation, Health Research Authority.
Professor Mahendra Patel: Inclusivity and Diversity Lead, Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences, University of Oxford.
Andy Rees: Clinical Trials Operations Manager, NHS DigiTrials.
Dr Simon Royal: National Specialty Lead for Primary Care, NIHR CRN Coordinating Centre.
Dr Nick Thomas: Specialty Lead for Primary Care, CRNThames Valley and South Midlands.
Dr Emma Tonner: National Medical Director's Clinical Fellow, NIHR CRN Coordinating Centre.
Dr James Williamson: Research Delivery Lead, NIHR CRN Coordinating Centre.

Appendix 2. Operational Oversight, and Meeting Structure

A number of different cross-stakeholder meetings were convened to support the planning, set-up and delivery of PANORAMIC, to ensure a collaborative approach to activities and facilitate information sharing and collective issue resolution. Further information is detailed in Table 2 below:

Meeting Name	Attendees	Purpose	Timeline
NIHR CRN, Study Team, DHSC ATTF and Funders meeting	NIHR CRN core team. Study Chief Investigators. Senior Trial Manager. NIHR Funder Representative. DHSC Antiviral Taskforce (ATTF) Representative. Lead LCRN Staff. Lead LCRN Specialty Lead for Primary Care.	● To coordinate study delivery. ● To monitor progress. ● To identify challenges. ● To provide a space to discuss delivery confidentially. ● To enable funders to keep abreast of delivery and issues.	Weekly from 13 October 2022 until 3 January 2023.
PANORAMIC Trial Management Group	Study Team. Study Co-Applicants incorporating: ● NIHR CRN National Specialty Lead for Primary Care/Deputy Medical Director. ● Lead LCRN Specialty Lead for Primary Care.	● Trial Management Group (TMG) Charter (specific to trial).	Weekly from start of study until May 2022; then fortnightly (ongoing).
PANORAMIC Joint Clinical and RDM Meeting (merger of	NIHR CRN core team. Study CI and Trial Manager. NIHR CRN Primary Care Research Delivery Managers	● To feed back on study progress to sites. ● To enable feedback sharing from sites to the	Weekly from 6 January 2022 to 27 March 2024.

Clinical Meeting and RDM Meeting)*	(RDMs) . Site Representatives (including clinicians). DA Network Representatives (including clinicians).	study team. ● To identify challenges and blockers. ● To brief sites on the use of digital recruitment tools.	

Table 2. An outline of the meetings attended by the NIHR CRN core team to support the set-up and delivery of the PANORAMIC trial *Note that this meeting began as two separate meetings from 24 November 2021, before being merged on 6 January 2022.

In addition to those outlined above, there was a large number of *ad hoc* meetings convened to discuss study set-up and progress, as required. It is notable that the approaches used for the meetings outlined above mirrored broader UPH meetings convened for other COVID-19 studies during the pandemic period.

The regular meeting between the study team, funder, and the NIHR CRN included a COVID-19 ATTF representative and was considered to be important to share key messages, and provide regular feedback and awareness of timelines. This collaborative approach also provided an opportunity for escalation of specific issues that arose during the rapid delivery of the study, and gave the ability for the trial to flex with changes in Government policy.

In addition, NIHR CRN representatives joined the weekly joint communications meetings about PANORAMIC (alongside colleagues from the study team, and NIHR and DA communications teams), the weekly NHSE delivery meetings, and the ATTF programme and strategy boards. While these meetings were not organised or hosted by the NIHR CRN, they proved invaluable in supporting study delivery. It is notable that these meetings, convened by the DHSC, included both a research update and a deployment update, as NHSE prepared for deployment of individual drugs should the results of PANORAMIC demonstrate clinical effectiveness.

The PANORAMIC RDM, Clinician, and Joint Clinical and RDM Meetings proved to be important meetings and enabled efficient and prompt messaging between the operational teams and the study team, facilitated by the NIHR CRN core team. Over the course of the study, the frequency of meetings was amended to reflect the pressures on the system and the need for urgent decision-making, whilst also providing opportunities for participating sites to directly ask questions of the study team, and to receive confidential advance notice of the results of the trial. To share responses and advice from the study team more widely, questions from participating sites were collated into an FAQ document, which was shared with the study team who provided responses to enquiries. These responses were then shared back with the participating site teams.

This support model, due to its intensity, may not be sustainable in the medium-term, but could be scaled-back and yet provide NIHR RDN support to nationally-important studies delivered at scale in the future. Clinical input into study delivery, as demonstrated in the clinical link role, was also beneficial to this primary care study, and is being considered for incorporation into ways of working across the NIHR RDN moving forward.

Appendix 3. A Diagrammatic Summary of PANORAMIC Recruitment

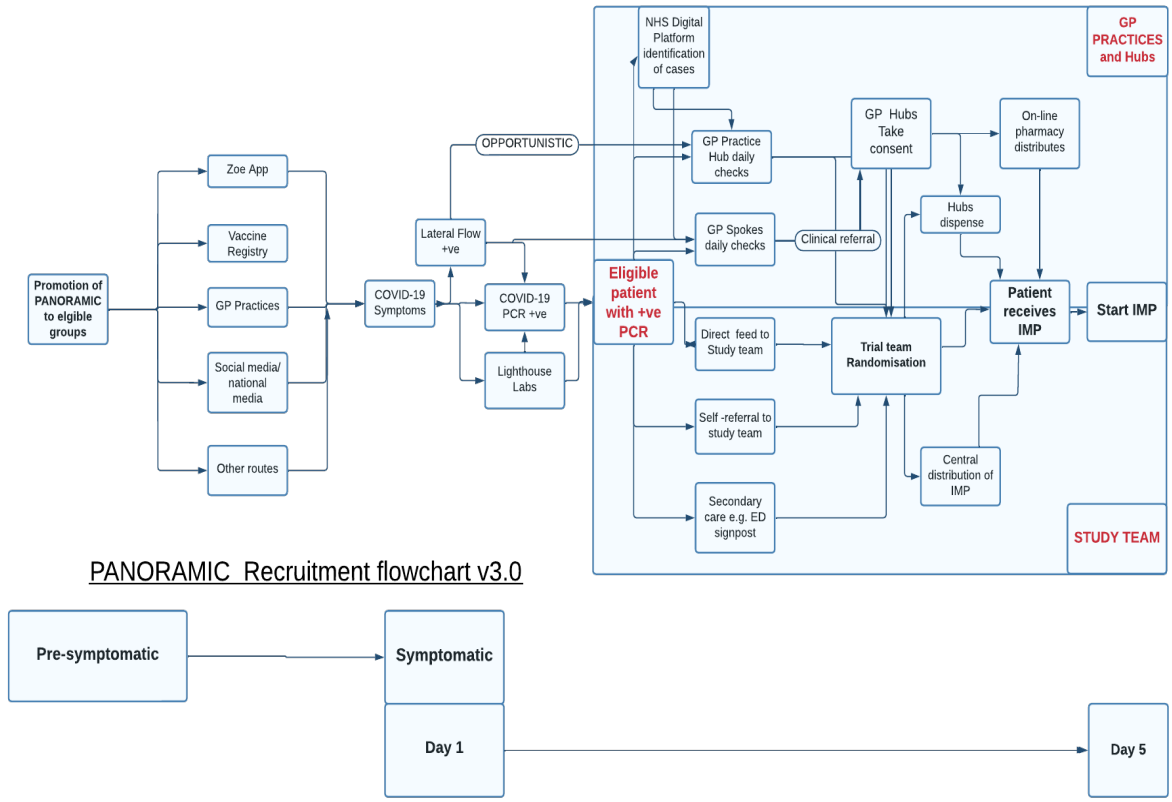

Fig 14: A Diagrammatic Summary of PANORAMIC Recruitment

Appendix 4. Comments and Updates from the HRA on Regulatory Activity related to the PANORAMIC Study

The HRA were committed to demonstrate and encourage proportionality and consistency, in their own reviews and through their guidance to others. While questions of liability were raised by sites when it was perceived that the pandemic situation might be resulting in unusual regulatory flexibility, the HRA sought to reassure sites by referring to the UK Policy Framework for Health and Social Care statement that "*The HRA indemnifies NHS research sites that accept assurances from the HRA against any claim covered by the NHS Litigation Authority arising as a result of incorrect assurances. If an NHS organisation undertakes its own checks that duplicate the assessments made by the HRA, the organisation will be liable for its own decisions made on the results of those checks and any consequences of those decisions.*"

The HRA is continuing to explore questions relating to the common law duty of confidentiality, raised by PRINCIPLE / PANORAMIC and more broadly during the pandemic, including with the Health and Care Information Governance Panel that produces guidance around concepts such as 'the direct care team', including in a research context, on its NHSE IG Portal. The HRA is also involved in discussions with the Office of the National Data Guardian – another Panel member – on when reasonable expectations are created in patients' minds that their data may be shared for care purposes (including in scenarios involving research as care). Gathering of

evidence about the same, including as part of a public consultation exercise under development, may help justify and encourage wider sharing of patient data than currently takes place in ways that still comply with the common law duty of confidentiality. This is highly relevant to the delivery of primary care studies.

The HRA acknowledges that governance is a complex field, and factors such as Information Governance, Data Protection, and UK GDPR cause anxiety. The HRA is considering how to make elements of their central review more visible, to provide greater reassurance and to aid study activities. Messaging is key, but this is not always easy. The release of a joint statement (HRA, CRN & R&D Forum, 2023) may have gone some way to addressing this issue but the HRA is considering what more can be done. This includes planning further engagement with the research community to understand how to target these messages to the right people, as part of its IG updating programme to be launched shortly (2024).

Appendix 5. Funding and Costing Challenges Encountered within the PANORAMIC Study.

Further to information outlined in Section 10.11, the following aspects were also encountered during the set-up and recruitment for PANORAMIC:

- Issues with initial preparation of the costings for PANORAMIC.
- Validity of costings under DHSC's AcoRD guidance (Attributing the costs of health and social care research) for Hub and Spoke models.
- Variation of remuneration between the costing document and contract.
- Moveable study delivery method.
- Change in IMP and implications.
- Number of different recruiting strategies.
- Changes in delivery and patient identification.
- Limitation of the Schedule of Events Cost Attribution Template (SoECAT) costing Template for Platform Studies.
- Design of payment structure.
- Variation in employment status for staff undertaking study activities.
- Virtual research ward remuneration.
- Funding of the central CTU recruitment team.
- LCRN concern of scale of potential Service Support Costs (SSCs) requiring payment during financial year 2022/23 for the Paxlovid arm.

Appendix 6. Excess Treatment Costs (ETCs), and PANORAMIC

Although no ETCs were incurred in PANORAMIC, under AcoRD potential ETC costs could be:

- Cost of the IMP itself.
- The following local management IMP activities as described in AcoRD Annex B costs:

- Manipulating the drug in such a manner that requires a Manufacturing and Import Authorisation (MIA) IMP licence. The MHRA defines these as 'Manufacturing' or 'Assembly'.
- Dispensing of the IMP / NIMP, including reconstitution, serial dilution as part of the act of physically dispensing and aseptic dispensing.
- All activities associated with the supply chain, including shipping, transporting, storing and disposal.

Appendix 7. The Different Media Routes used in Promotion of the Study

<table>
<tr><th colspan="3">Media</th></tr>
<tr><td>National radio stations
e.g.. Times Radio.

Regular and frequent slots with Talk TV and radio; Times Radio.</td><td>Local radio
Regular slots as a contributor on BBC Radio Leeds, Sheffield, Bradford and York, reaching out to listeners on Sunday evenings.

BBC Radio Lancaster.
Link FM Sheffield.</td><td rowspan="2">Mixed media
Asian Media Group through its various publications to help promote the trial. This is the largest Asian media group in the UK and supported the trial throughout its promotions.

Newspapers and Press
Asian Media Group.
Asian Standard.
The Asian Today.
Eastern Eye.
The i (Independent).
Metro.
Asian Voice.
Gujarat Samachar.
Garavi Gujarat.

Pharmacy Press
Pharmaceutical Journal.
Pharmacy Business.
Chemist + Druggist.
The Pharmacist.

Local press:
Telegraph and Argus.
Yorkshire Post.
Wakefield Express.
Eastern Eye.
Paigam.</td></tr>
<tr><td>National TV
Sky TV's Islam Channel - Health Matters. This is the most-watched Islamic TV channel in the UK. This involved a live one-hour interview in conjunction with the MCB and BIMA as the topic of the week for their Health Matters programme.

Kanshi TV reaching out to UK Punjabi viewers.
Sky News.
Al Jazeera.</td><td>Regional TV
BBC Look North.
ITV News Calendar.

YouTube
Kanshi TV in Birmingham through its studios, where Professor Mahendra Patel promoted COVID-19 studies in Punjabi to all its viewers on several occasions.</td></tr>
</table>

Social media		
Twitter *(now X)* examples	**WhatsApp group examples**	**Instagram examples**
British Islamic Medical Association. Muslim Council of Britain. BAPS Neasden Temple. British Association of physicians of Indian origin (BAPIO). Muslim doctors Cymru Young advocates for disability NHS Chief Pharmaceutical Officers, England, Wales, Scotland and Northern Ireland NHS England. Oxford University's Nuffield Department of Primary Care Health Sciences. Royal Pharmaceutical Society. South Asian Health Foundation. UK Black Pharmacists Association. General Pharmaceutical Council. Nepalese Nurses Association UK. Medical Association of Nigerians Across GB. Tanzanian UK Health Diaspora Association (TUHEDA).	BAPIO. BAPIO NW. APNA NHS National Group. Guild of Healthcare Pharmacists. Bradford Hindu Council.	Royal Pharmaceutical Society. Indian Pharmaceutical Association Students' Forum (IPA-SF). University of Bradford.

Influencers	
Mr Motivator TV celebrity Jamaican-born Derrick Evans, alias Mr Motivator, developed a video and seven posters, one for each day of the week, promoting the PANORAMIC trial through	**Lady Anne Welsh** The entrepreneur and patient advocate for sickle-cell conducted a live Instagram video with her large following, which attracted nearly 10,000 attendees, highlighting the

social media and the Oxford trial website (see Figure 14B).	importance of engaging with the trial and reaching out to people of black and ethnic minority origin.

Table 3: The Different Media Routes used in Promotion of the Study

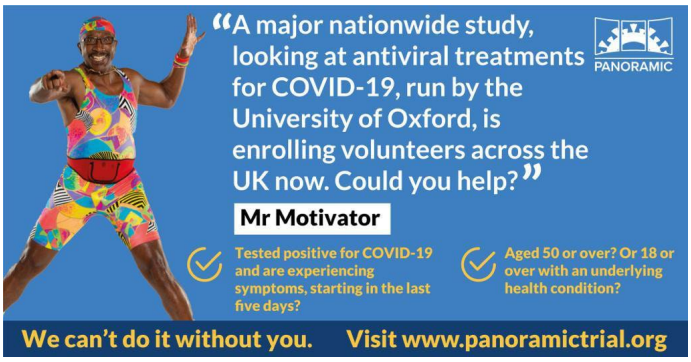

Figure 15A. (left) Advert for PANORAMIC live interview on Islam Channel's Health Matters programme. Figure 15B. (right) PANORAMIC trial poster developed by and featuring Derrick Evans, alias Mr Motivator.

18. Glossary

Agile Delivery Team

Agile Delivery Teams comprise staff from a broad range of backgrounds with significant experience in delivering research in a range of settings and across a number of specialisms. Agile Delivery Teams seek to increase opportunities for patients to take part in health and social care research and are funded and act on behalf of the NIHR CRN. [Ref]

AGILE Clinical Trial Platform

AGILE is a collaboration between the University of Liverpool, Southampton CTU, and other external partners. The team includes Infectious Diseases clinicians, clinical and pre-clinical pharmacologists, clinical trials specialists and statisticians, each bringing a unique set of skills and expertise to design the best platform possible. [Ref]

Attributing the cost of health and social care Research & Development (AcoRD)

The AcoRD guidance provides a framework for the NHS and its partners to identify, recover and attribute the costs of health and social care research and development, in a transparent and consistent way. [Ref]

Antivirals and Therapeutics Taskforce (ATTF)

The ATTF was a DHSC-led group responsible for the coordination of the end-to-end provision of treatments for coronavirus (COVID-19) in the UK. Its responsibilities included identifying potential COVID-19 therapeutics, trialling these as part of an advanced programme of clinical trials, and making effective treatments available to UK patients. The ATTF was formally closed on 31 March 2023 in line with the government's strategy of living with COVID-19. [Ref]

Central Portfolio Management System (CPMS)

A cloud-based system that holds the NIHR Clinical Research Network (NIHR CRN) Portfolio, as well as the network portfolios of Northern Ireland, Scotland and Wales. [Ref]

Clinical Research Facilities (CRF)

NIHR's 28 Clinical Research Facilities (CRFs) are purpose built facilities in NHS hospitals where researchers can deliver early-phase and complex studies. [Ref]

Clinical Trial Agreement (CTA)

Often called model agreements or model Clinical Trial Agreements (mCTAs), one of two UK-wide tools required to complete the National Contract Value Review (NCVR) - the UK's standardised, national approach to costing and contracting for commercial contract research. [Ref]

Clinical Trial of an Investigational Medicinal Product (CTIMP)

A clinical trial that is within the scope of the UK Medicines for Human Use (Clinical Trials) Regulations 2004. An investigation in human subjects, other than a non-interventional trial, intended: a) to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products, b) to identify any adverse reactions, or c) to study

absorption, distribution, metabolism and excretion, with the object of ascertaining the safety and/or efficacy of those products. [Ref]

COPI Notices
Notices issued by the Secretary of State for Health and Social Care under the Health Service (Control of Patient Information) Regulations 2002 (the COPI Notices) requiring certain organisations to disseminate confidential patient information for specific purposes related to the pandemic response. [Ref]

COVID-19 Medicine Delivery Units (CMDUs)
A government commissioned unit established to provide access to COVID-19 therapeutics for non-hospitalised patients at the highest risk, as per the NHS COVID-19 pandemic response. [Ref]

EMIS Health
EMIS Health, formerly known as Egton Medical Information Systems, supplies electronic patient record systems and software to primary care. [Ref]

Excess Treatment Costs
A research study may result in care that differs from standard treatment in the NHS or is delivered in a different location. The associated NHS treatment costs may be less than or greater than the cost of standard treatment. If greater, the difference between the NHS treatment costs and the cost of the standard treatment is referred to as the NHS Excess Treatment Costs (ETCs). [Ref]

General Data Protection Regulation (GDPR)
A European Union regulation on information privacy in the European Union (EU) and the European Economic Area (EEA). [Ref]

Good Clinical Practice (GCP)
A set of internationally recognised ethical and scientific quality requirements that must be followed when designing, conducting, recording and reporting clinical trials that involve people. [Ref]

HEAL-COVID Trial
HElping Alleviate the Longer-term consequences of COVID-19 (HEAL-COVID): A national platform trial - IRAS ID: 294861. Research question: Can interventions in the convalescent phase of COVID-19 improve longer-term outcomes? [Ref]

Health Research Authority (HRA)
An NHS organisation established to protect and promote the interests of patients and the public in health research. [Ref]

Investigational Medicinal Product (IMP)
The MHRA defines as follows:

An investigational medicinal product is any medicinal product which is being tested within a trial or any product, including placebo, used as a reference in a clinical trial. This includes products with a marketing authorisation where the product is:

- *used in a different form from the marketing authorisation.*
- *used for an indication not included in the summary of product characteristics for that product or*
- *used to gain further information about the product as authorised in the clinical trial authorisation.*

[Ref]

Integrated Care Board (ICB)
Statutory organisations that bring NHS and care organisations together locally to improve population health and establish shared strategic priorities within the NHS. [Ref]

Livi
Livi is a digital healthcare service by Kry International AB, a Swedish online healthcare company based in Stockholm. [Ref]

Local Clinical Research Network (LCRN)
The Local Clinical Research Networks were overseen by the National NIHR Coordinating Centre and supported clinical research infrastructure throughout England. The lead LCRN for PANORAMIC was CRN Thames Valley and South Midlands. The local Networks helped to increase the opportunities for participants to take part in clinical research, ensured that studies are carried out efficiently, and supported the Government's Strategy for UK Life Sciences by improving the environment for commercial contract clinical research. As of April 2024 the NIHR Clinical Research Network will transition into the NIHR Research Delivery Network (RDN), and in October 2024 the LCRNs will be transitioned into the new Regional Research Delivery Networks (RRDNs). [Ref]

Local Portfolio Management System (LPMS)
Regional systems for collating research intelligence. [Ref]

Medicines and Healthcare products Regulatory Agency (MHRA)
The Medicines and Healthcare products Regulatory Agency regulates medicines, medical devices and blood components for transfusion in the UK. [Ref]

Non Investigational Medicinal Product (NIMP)
A medicinal product which is not classed as an IMP in a trial, but may be taken by subjects during the trial. [Ref]

Participant Identification Centres (PICs)
Organisations from which clinicians or clinical units refer potential participants to a research team based in another organisation, for assessment and possible recruitment to a study. [Ref]

Primary Care Networks (PCNs)

A group of GP practices working closely together, aligned to other health and social care staff and organisations, providing integrated services to their local population. [Ref]

RECOVERY Trial
An international clinical trial identifying treatments that may be beneficial for people hospitalised with pneumonia, which started in the UK in 2020 as the *Randomised Evaluation of COVID-19 Therapy*, a clinical trial testing treatments for people admitted to hospital with COVID-19 pneumonia. [Ref]

REMAP-CAP
A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia. An international platform trial embedded in critical care that investigated the best range of treatments for severely ill patients with COVID-19. [Ref]

SoECAT
A Schedule of Events Cost Attribution Template (SoECAT) for clinical research is a spreadsheet-based application whose purpose is to capture the different activities associated with clinical research at the research site level and attribute them accordingly as 'research activities', 'support activities', or 'treatment activities', in line with the national guidance document 'Attributing the Costs of Health and Social Care Research and Development' (AcoRD). [Ref]

SNOMED
SNOMED CT is a structured clinical vocabulary for use in an electronic health record, using UK general practice electronic health records. [Ref]

SystmOne
A clinical informatics system designed by The Phoenix Partnership (TPP) which enables clinicians to access a single source of information detailing a patient's contact with health services across their lifetime. [Ref]

Trial Steering Committee
The role of the Steering Committee is to provide overall supervision for a project on behalf of the study's Sponsor and Funder and to ensure that it is conducted to the rigorous standards set out in the UK Policy Framework for Health and Social Care and the Guidelines for Good Clinical Practice. [Ref]

UK COVID-19 Therapeutics Advisory Panel (UK-CTAP)
UK-CTAP was part of the Clinical Trials Infrastructure National Core Study, formed to accelerate delivery of large scale trials for COVID-19 treatments. The role of UK-CTAP was to consider potential COVID-19 treatments proposed through an open nominations portal. The portal and proposal process was managed by a UK Research and Innovation (UKRI) team. [Ref]

Urgent Public Health (UPH) Group

The Urgent Public Health (UPH) Group was convened by the National Institute for Health Research (NIHR) Clinical Research Network (CRN), was chaired by the Medical Director (NIHR CRN), and aimed to prioritise COVID-19 research studies to be delivered through the NIHR CRN. The group included clinical experts from across clinical specialties and settings, methodologists and other key individuals from across NIHR Translational Research Collaborations; Medtech and In Vitro diagnostics Co-operatives; Biomedical Research Centres; the UK Clinical Research Collaboration; Clinical Trials Unit (CTU) Network; Devolved Administrations (DAs); patient and public engagement groups; Public Health England; DHSC; and NHS England (NHSE).

Applications to the UPH Group were made through an online portal and were assessed for scientific value, deliverability in the existing environment, appropriateness of scope and scale, and the ability to deliver game-changing results relevant to the pandemic. Recommendations regarding UPH designation on an individual study basis were then provided to the Chief Medical Officer (CMO) via DHSC.

Virtual Ward

A virtual ward (also known as hospital at home) is typically defined by NHS England as an environment "*allowing patients to get hospital-level care at home safely and in familiar surroundings, helping speed up their recovery while freeing up hospital beds for patients that need them most.*" However, for the purpose of the PANORAMIC study, the term 'NIHR CRN virtual research ward' meant "*a ring-fenced virtual environment of NIHR CRN staff to assist the CTU*". [Ref]

Vision

A clinical system designed by Cegedim that helps practices deliver all aspects of business and patient care and is one of the minority clinical systems in UK general practice. [Ref]