



# Large scale clinical trials: lessons from the COVID-19 pandemic

Alex R Horsley <sup>1</sup>, Laurence Pearmain,<sup>1,2</sup> Sean Knight,<sup>1,3</sup> Nick Schindler,<sup>4,5</sup> Ran Wang,<sup>1</sup> Miriam Bennett,<sup>1</sup> Rebecca C Robey,<sup>1</sup> Jane C Davies,<sup>6</sup> Ratko Djukanović,<sup>7</sup> Liam G Heaney,<sup>8</sup> Tracy Hussell,<sup>9</sup> Stefan J Marciniak <sup>10,11</sup>, Lorcan P McGarvey,<sup>12</sup> Joanna Porter,<sup>13,14</sup> Tom Wilkinson,<sup>15</sup> Chris Brightling <sup>16</sup>, Ling-Pei Ho<sup>17,18</sup>

**To cite:** Horsley AR, Pearmain L, Knight S, *et al*. Large scale clinical trials: lessons from the COVID-19 pandemic. *BMJ Open Res Res* 2022;**9**:e001226. doi:10.1136/bmjresp-2022-001226

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjresp-2022-001226>).

Received 6 February 2022  
Accepted 14 May 2022

## ABSTRACT

**Background** The COVID-19 pandemic has presented substantial new challenges to clinical and research teams. Our objective was to analyse the experience of investigators and research delivery staff regarding the research response to COVID-19 in order to identify these challenges as well as solutions for future pandemic planning.

**Methods** We conducted a survey of diverse research staff involved in delivery of COVID-19 clinical trials across the UK. This was delivered online across centres linked to the NIHR Respiratory Translational Research Collaboration. Responses were analysed using a formal thematic analysis approach to identify common themes and recommendations.

**Results** 83 survey participants from ten teaching hospitals provided 922 individual question responses. Respondents were involved in a range of research delivery roles but the largest cohort (60%) was study investigators. A wide range of research experiences were captured, including early and late phase trials. Responses were coded into overarching themes. Among common observations, complex protocols without adaptation to a pandemic were noted to have hampered recruitment. Recommendations included the need to develop and test pandemic-specific protocols, and make use of innovations in information technology. Research competition needs to be avoided and drug selection processes should be explicitly transparent.

**Conclusions** Delivery of clinical trials, particularly earlier phase trials, in a pandemic clinical environment is highly challenging, and was reactive rather than anticipatory. Future pandemic studies should be designed and tested in advance, making use of pragmatic study designs as far as possible and planning for integration between early and later phase trials and regulatory frameworks.

## INTRODUCTION

COVID-19 represents the first global pandemic of the modern era. Clinical features of the earliest cases from Wuhan were published in February 2020, and included fever and cough associated with pneumonia and acute respiratory distress.<sup>1,2</sup> The first UK cases of the novel beta-coronavirus SARS-CoV2 were confirmed

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The COVID-19 pandemic placed unprecedented pressures on research, both in terms of design and delivery, and had not been widely planned for in advance. Research was essential to improving care and outcomes but in many cases was piecemeal and low quality.

### WHAT THIS STUDY ADDS

⇒ We have documented the experience and recommendations of a large number of investigators and research delivery staff with diverse experience. Among many successes, they identified that clinical trials need careful design for pandemic environments, advance testing, transparent drug selection processes and better use of information technology innovations.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Future pandemics are likely, and an integrated research response is an important aspect of advance planning. The observations and recommendations here will help prepare for future infections, but can also be applied to any research taking place in acute clinical settings. For pandemics, research integrity and efficiency would be maximised by pre-planning and testing protocols, by linking an integrated early to late phase programme to regulatory approval, and by improving consent and information processes.

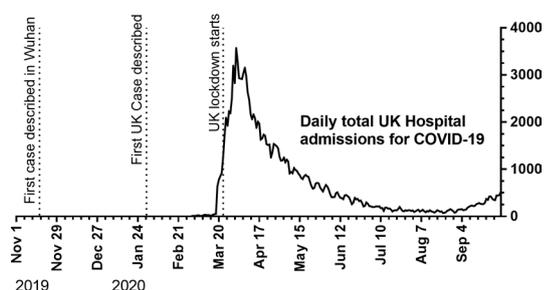
on 30 January 2020, the same date that the WHO declared a public health emergency. Infection within the UK had become widespread by March 2020.<sup>3,4</sup> The rapid spread of SARS-CoV2 caused widespread disruption across society and healthcare, and left little time for planning and design of research to respond to the challenge (figure 1). Some studies (eg, ISARIC, REMAP-CAP<sup>5,6</sup>) had pre-existing protocols that could be adapted to COVID-19, but in most instances new study protocols were necessary.



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

**Correspondence to** Professor Alex R Horsley; alexander.horsley@manchester.ac.uk



**Figure 1** Timeline of first wave of COVID-19 pandemic, showing total UK daily hospital admissions. Source: [coronavirus.data.gov.uk/details/healthcare](https://coronavirus.data.gov.uk/details/healthcare).

COVID-19 research studies had to rapidly adapt to the unique environment and challenges created by the pandemic. This included evolving hospital infection control practices, staff absence and isolation, restricted laboratory use and reduced research space due to social distancing. Staffing and research resources were limited by reallocations necessary to support the clinical care of escalating inpatient cases. Patients were isolated, often very ill and struggled to follow complex study information sheets. From a practical perspective therefore, conventional trial delivery and regulation were likely to be poorly suited to the pandemic.<sup>7</sup>

Though hugely disruptive to conventional clinical trials and research, the response to the pandemic offers an opportunity for innovation and learning which can be used to better prepare for future pandemic planning. In particular, the RECOVERY study (NCT04381936), a large-scale pragmatic study, has been exceptionally successful and has dominated the research ecosystem. Greater challenges, however, were experienced by other research initiatives, and recruitment to early-phase platform studies has been much slower. We were interested to learn what aspects of the research response were successful, and what areas presented significant challenges. To explore this, we conducted a UK-wide qualitative survey of research staff involved in COVID-19 trials. This was distributed through all ten respiratory Biomedical Research Centres and affiliate organisations by the Respiratory Translational Research Collaboration (R-TRC). Here, we present an analysis of the survey using formal thematic review methods and interpretation of the findings in order to inform planning for future pandemic response.

## METHODS

An online survey was developed to capture the experience of a range of respondents involved in the design and delivery of COVID-19 research studies. The survey consisted of 21 questions divided into seven sections structured around key features of clinical trials (see online supplemental file). These were defined explicitly as ‘clinical trials or any relevant research studies’. For each section respondents were asked: what worked well, what features did not work well, and recommendations

they would make for future studies. Questions were developed by the corresponding authors, in accordance with guidance for qualitative questionnaire development,<sup>8</sup> and reviewed and refined by the R-TRC clinical academic leads. The survey was piloted prior to use.

Sampling was purposive, aiming to capture a representative sample of the R-TRC associated workforce, across all levels of clinical trial design, development and delivery. R-TRC leads from each centre distributed the questionnaire to staff who had worked on clinical trials and/or related experimental medicine COVID-19 studies. The survey was open between 14/ April 2021 and 18 May 2021. Response was voluntary and formal ethical approval not required, per Medicines Health Regulatory Authority (MHRA) research ethics tool ([www.hra-decisiontools.org.uk](http://www.hra-decisiontools.org.uk)). As this study was directed at staff experiences of pandemic research, patient and public involvement was not included.

## Data analysis

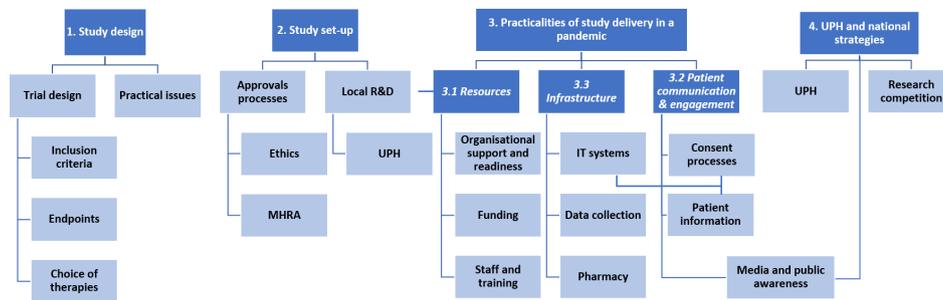
A reflexive, inductive, thematic analysis approach was employed, following the Braun and Clarke six-step approach to code and construct themes<sup>9</sup> and reported in line with the Standards for Qualitative Research.<sup>10</sup> Each section was independently reviewed by two reviewers who familiarised themselves with the data by reading and rereading the responses. Themes were generated by analysing for patterns of naturally occurring clusters of response coding with high frequency of occurrence, allowing respondent data to shape themes. Common themes were identified, often appearing in answers to more than one questionnaire section.

## Positionality

Responses have been interpreted in the context of the authors’ backgrounds and experience of pandemic study research and clinical trials (see online supplemental file). Those coding responses were respiratory specialists with experience of respiratory research pre-pandemic, as well as experience in treating and researching COVID-19. Best practice in analysing survey response data was followed,<sup>11</sup> including: (1) the use of focused questions designed specifically to address the aims of this study; (2) robust, systematic analytical procedures to facilitate insights into the pandemic research response; (3) consultation with an experienced qualitative researcher (NS) who assisted with study design and provided guidance in conducting the analysis.

## RESULTS

Eighty-three survey participants across 10 centres in England and Northern Ireland provided 922 responses. Sixty per cent (n=50) of respondents were clinicians and/or academic researchers, with the majority involved in study recruitment and clinical care during the COVID-19 pandemic (online supplemental table 1). Of these, 50% (n=25) had experience in leading COVID-19



**Figure 2** Thematic domains presented for review are shown in dark blue boxes, including the three subdivisions of domain 3. Response themes that contributed to these domains are shown in lighter blue, including subthemes that fed into these. Where themes contributed significantly to more than one domain this is also indicated. IT, information technology; MHRA, Medicines and Healthcare Products Regulatory Agency; R&D, Research and Development department. UPH, Urgent Public Health group.

trials or in trial design and conception. Other important research delivery roles represented included research nurses (n=12, 14%), research pharmacists (n=4, 5%) and research managers and administrators (n=12, 14%). Specialist roles represented included: research statisticians, physiotherapists, physiologists and basic scientists. Experience in trials was extensive across experimental medicine, phase 2 and 3 clinical trials. Trials/studies respondents worked on included: RECOVERY (n=52, 62%),<sup>12–15</sup> ACCORD (Eudract: 2020-001736-95) (n=24, 29%),<sup>16</sup> CATALYST (EudraCT: 2020-001684-89) (n=13, 16%),<sup>17</sup> Synairgen (NCT04385095) (n=10, 12%),<sup>18</sup> TACTIC (NCT04390464) (n=4, 5%),<sup>19</sup> Theravance (NCT04402866) (n=3, 4%) and Remdesivir (n=9, 11%).

### Thematic analysis of survey responses

Although survey questions were presented in categories identified *a priori* as representing discrete domains of study activity, responses were less discretely portioned. To resolve this, the analysis used the original question category as a framework, but grouped common themes in answers into a revised schedule of four different domains. One of these ('practicalities of research delivery in a pandemic') was subdivided into three sub-domains. A simplified representation of the four domains is shown in figure 2. Representative quotes from respondents are presented in the boxes.

#### Domain 1: study design

Designing a study for effective delivery in the COVID-19 pandemic clinical environment posed a range of new challenges. This was reflected in the survey, where respondents were united in approval, and recommendation of, pragmatic study designs (studies that run alongside clinical care), as exemplified by the RECOVERY trial (see box 1). Platform and adaptive designs used in phase 2 and 3 trials were also almost universally recommended, since these were seen to enable rapid evolution of therapeutic options without requiring new study setup.

Other features highlighted as important in trial design were: minimising data collected, reducing restrictions on

recruitment, and developing processes to make consent easier. Pragmatic and clear inclusion criteria and provision of concise patient information sheets (PIS) were praised, as were information technology (IT) solutions used successfully to reduce duplication of work and minimise infection risk. These included: electronic data collection tools, telemedicine and measurements patients could self-perform.

However, there were large variations in how well individual studies dealt with these challenges. Some protocols were not well tested prior to dissemination, resulting in lack of clarity, confusion and numerous amendments. Practical considerations of pharmacy delivery were not incorporated sufficiently into some study designs. Examples included pharmacy manuals released after protocol amendments and poor adverse event and safety follow-up plans for some studies. Overlooked practical

#### Box 1 Selected representative quotes from respondents, referring to study design and setup

##### Domains 1 and 2: selected quotes on study design and set-up

- 'Simple pragmatic studies worked best'
- 'Studies that had taken time to engage with both patients and clinicians who actually clinically managed patients with COVID and understood the clinical context, were significantly better...'
- 'Some studies were rushed out and did not have databases or CRFs in place at the start, which meant that it was not clear what data should be collected, and some was missed.'
- 'Overzealous monitoring by commercial companies/ CRA's.' .... worked poorly
- 'There was an absence of attempt at harmonisation across study protocols and ability or willingness to share data between studies in some instances.'
- 'Streamlined ethics and regulatory reviews a revelation'
- 'Online meetings and site initiation visits, good communication'
- 'Complex clinical research organisation arrangements with multiple lines of communication worked poorly'
- 'Not enough engagement at the start with clinicians'
- 'The rapidity of set up meant that some processes weren't completely thought through in advance.'

considerations indicate a need to properly engage and include patient-facing clinicians, research nurses, allied health professionals (eg, physiotherapists) and pharmacists in designing studies.

### Domain 2: study setup

During the first wave of the pandemic, the National Research Ethics Service (NRES) and MHRA implemented emergency processes to speed study review and approval. Respondents overwhelmingly found this rapid approval process a step-change improvement. Principal investigator (PI) respondents were effusive about the speed and simplicity of the process, and reductions in perceived bureaucracy (see [box 1](#)). Early on, there were problems noted in gaining approvals to access electronic patient data.

Speed of study setup once approved was also considered impressive by the majority of respondents. Online site initiation visits, and meetings and training by video-conferencing were credited with improving efficiency. Feedback suggests little was lost in this transformation.

Local approvals and systems, however, were not always reconfigured to the same extent. Hospital research (Research and Development, R&D) departments had a high volume of studies to deliver with reduced staff in a limited time. Comments regarding speed and efficacy of local R&D contributions varied, attracting both strong praise and criticism. In many cases this reflected specific experiences and local issues, but overall the most common complaint was of multiple studies being set up simultaneously. Delays at the level of local R&D were the most common reason for hindrance in study set-up. More oversight, by working groups or a national coordinating R&D body, were favoured solutions proposed.

Contract research organisation involvement was highlighted as an exception to overwhelmingly positive experiences of fast setups, with respondents finding communication and negotiations protracted and complex. Data monitoring was also often challenging. Initial light touch monitoring subsequently became more complicated, with the standards required being poorly suited to collection of data in an acute environment.

### Domain 3: practicalities of research delivery in a pandemic

#### Resources

The national effort was pivoted to providing clinical care and many clinical academics were redeployed to front-line clinical duties. This created a lack of research-experienced staff to lead trial recruitment, a problem in particular for the more complex studies where time is needed to screen and consent patients properly. Respondent recommendations included provision of protected, allocated time for clinicians to contribute to studies and facilitating release of clinical academics with relevant expertise. Resource limitations meant clinical versus research tensions were similar across other disciplines, for example, increased pharmacy clinical workloads also impacted trials support ([box 2](#)).

### Box 2 Selected representative quotes from respondents, referring to issues of study delivery

#### Domain 3: selected quotes on practicalities of research delivery in a pandemic

'Dedicated research nurse support with seven day a week accessibility was a singular factor for success in recruitment'

'Some very important studies came with limited funding'

'Not enough staff during the peak to consent and recruit'

'Phase 2 consents were long and arduous. Hard for patients to understand and really follow, often could not take in the information being presented'

'Those studies which focused on having a pragmatic consenting process were easy to recruit to and did not over-burden patients who were acutely unwell'

'...recruitment of non-English speakers could have been improved - and the translated leaflets didn't seem to be particularly helpful.'

'(Recommend) streamlining requirements for participant information in line with what participants really feel they need to decide on consent'

'Invest in infrastructure for digital consent.'

'Work with ethics specialists on how we can shorten informed consent'

'Online training videos worked well as they were easy and allowed accessibility for all'

'It was difficult to get information out of Red Zones as the intended IT solution did not work as well as expected and in the end had to be abandoned.'

'Hard to deliver nebulised drugs'

Increased funding was praised but also identified as insufficient and several studies were considered inadequately funded to cover running costs. Secondment of research staff from other areas was praised, but again felt to be too scarce for the pandemic research demands. Examples of mistakes to avoid included: redeploying clinical academic trainees; furlough of research and administrative staff; and failure to effectively use medical students.

Another significant resource constraint was patients. Admissions varied between extremes and at points there were few patients meeting phase 2 study entry criteria. With multiple competing studies, local research teams had to select which trial to prioritise, making recruitment difficult for others. Prioritisation was often uncertain on the ground and messaging not always clear.

#### Patient communication and consent

Many studies repurposed PIS and consent form templates originally designed for other studies. Complex and detailed information was often hard for patients to fully comprehend given their clinical and emotional state. Communicating this information through face masks was also challenging. Use of technology to support consent was not well established or delivered. While some respondents positively described using a tablet computer to deliver information and collect consent, others complained this was poorly designed and struggled with National Health Service (NHS) IT infrastructure. Respondents also

identified a lack of provision for PIS/consent forms in different languages, potentially excluding and discriminating against patients.

Respondents suggested simplifying PIS and consent forms by working with patients and other specialists to streamline them, while ensuring consent remained properly informed. There was support for new technologies such as e-consent and use of video to communicate patient information. A number of respondents suggested looking at opt-out or presumed consent, which would be suitable for observational studies. A centralised national research programme was proposed to enable recruitment to multiple studies through a single consent.

### Infrastructure

Impact of physical infrastructure on research delivery varied between organisations, with a number of specific local barriers highlighted. These included an erosion of physical administrative space close to clinical areas, and a lack of side-rooms or spaces with higher air exchanges per hour (necessary to deliver nebulised preparations).

As noted above, problems were often cited with NHS IT (systems and hardware) being unable to handle new solutions such as online meetings and e-consent. Despite this, the vast majority of respondents felt study set-ups should continue to incorporate IT innovations introduced to reduce unnecessary face-to-face contact between staff. Online access to study resources and data collection was praised, as were online peer-to-peer forums providing pharmacy support. Particular difficulties, however, were noted with electronic data collection and capture in emergency departments, thereby losing the opportunity to learn from milder patients who were not admitted. Respondents recommended using IT to address difficulties in obtaining physical signatures for delegation logs.

Capacity of pharmacy services to deliver COVID-19 studies was a local limitation some felt had been overlooked. A lack of aseptic pharmacy facilities at some study sites meant logistics became complex and caused practical difficulties in delivering certain trial treatments. These oversights in pharmacy capacity highlight a need to ensure allied health professionals are adequately represented at organisational and strategic level, echoing feedback from 'study design' responses.

### Domain 4: national organisation and prioritisation strategies

To prevent proposed therapies being administered to COVID-19 patients in an *ad hoc* manner, or as part of underpowered or poorly designed clinical trials, the UK Department of Health and Social Care endorsed a unified approach where experimental therapies would not be available unless part of a clinical trial. This approach was strongly supported and made it easier for clinicians and patients to understand the central role of research and trials (see [box 3](#)).

The mechanism to deliver this was via the Urgent Public Health Group (UPH) from the National Institute for Health and Care Research (NIHR), whose remit was

**Box 3** Selected representative quotes from respondents, referring to national strategies and prioritisation (Urgent Public Health, UPH)

#### Domain 4: Selected quotes on UPH and national strategies

'UPH process was unclear, slow and not transparent'  
 'There were too many competing studies and prioritisation was quite difficult'  
 'Smaller agile single centre studies were harder to get off the ground due to the precedent for national studies.'  
 'UPH badging and alignment between the phase II platforms was messy with no clear process'  
 'UPH was the right idea, but not perfectly deployed'

to ensure prioritisation and organisation of resource for COVID-19 clinical trials and studies in UK. This was set up in April 2020, shortly after the exponential first wave of infection. This created a two-tier system: for 16 studies with the top '1a' status there was rapid local NHS and NRES approval, as well as provision of funded nurses from NIHR CRN. For studies not awarded 1a status, there was little resource or staff support, making them essentially non-viable in many centres. Difficulties dealing with UPH was a theme strongly expressed by many respondents, particularly study investigators. Several respondents commented specifically that routes to UPH approval and reasons for decisions were not communicated effectively, and suspicion about how studies were badged was expressed by some respondents.

Multiple phase 2 platform study proposals subsequently emerged, with four eventually opening to recruitment. The theme of research competition was widely reported in the survey, noting that this led to competition for both staff and patient resources. From a patient perspective, this could lead to patients being provided with up to three trial protocols as well as protocols for non-interventional studies, an experience that could be overwhelming.

A national research strategy was recognised as an important component of the UK's research success in COVID-19, and many respondents offered suggestions on how to improve this. Having national trial platforms for both phase 2 and 3 studies already in place before a pandemic, and to have these clearly identified as the supported studies into which resource would be invested, was proposed as a means to avoid many of the issues and frustrations experienced by investigators. Several respondents also commented that the procedures for identifying therapies needed to be clearer and more transparent.

### DISCUSSION

In this thematic review, we have gathered the experiences of a large number of diverse investigators and research delivery staff to examine the research response to the COVID-19 pandemic in the UK. Although questions were focused on delivery of COVID-19 studies, the comments and learning also have relevance for clinical trials more



broadly. Key themes that emerged from this are described below.

### Planning for a pandemic before it occurs

There was consistent feedback from respondents, across multiple domains, that effective pandemic response planning starts well in advance of the threat itself.<sup>20</sup> Proposed trials would benefit from prior approvals, and—importantly—from rigorous prior testing of processes and data collection, all of which caused issues in early COVID-19 studies. Training packages could also be prepared, ready for dissemination via online delivery when required. Similar proposals have also been made to pre-establish vaccine trial protocols and teams which can then be rapidly mobilised to recruit from emerging hot-spots of infection.<sup>21</sup> Such an approach allows rapid setup and delivery, and significantly reduces time to trial readout. All delays ultimately impact on clinical outcomes and reducing these is an essential component of pandemic preparedness.

### An integrated research pathway

The success of the RECOVERY trial, and its prioritisation in many sites, inevitably occurred at the expense of early phase trials and experimental medicine in some. Local prioritisation and patient recruitment had a major impact on time to completion for early phase trials. Many respondents complained about the multiplicity of competing studies, creating pressures for staff and patients. We consider that the early phase trials space is a crucial area of consideration for future pandemic planning. Though hugely successful, the phase 3 RECOVERY trial has largely ruled treatments out, and only dexamethasone, tocilizumab, and monoclonal antibodies have been shown to improve survival.<sup>13 14 22</sup> Future pandemic planning should therefore ensure an integrated pathway from early phase studies through to larger pragmatic trials of efficacy. Advance planning of sites for early phase work would help concentrate expertise in specialist centres with the facilities and staff to deliver more complex studies.

### Design studies for the realities of the pandemic clinical environment

There was clear support for studies that are pragmatic and designed to interrupt clinical care as little as possible, a model exemplified by RECOVERY.<sup>23</sup> This will not be appropriate for many early phase studies, where more rigorous follow-up and patient selection are required, but study design even in these cases needs to reflect the limited staffing and clinical resources available. Such restrictions are also important for considering some of the broader practical aspects of trial delivery, which have been persuasively highlighted by respondents. Even for phase 2 studies, it is possible to ensure that eligibility criteria are kept as simple as possible, and that monitoring

and data collection are streamlined. Study design needs to incorporate diverse stakeholders including clinical delivery staff, allied healthcare professionals and patients.

### Making use of digital innovations

Innovations in digital technologies have the potential to greatly enhance efficiency of trial information and consent processes, and are well suited to work in a pandemic environment. It was understandable, given the rapid progression of the pandemic, that these were not well developed for COVID-19 studies, and many simply reproduced the paper forms. There exists, therefore, an opportunity to review how we deliver this information, including how much information is required for full consent, and explore how technology can improve the processes, widen access and increase efficiency. Digital solutions were also proposed for data capture. Although these already exist, many respondents expressed frustration at poor integration with hospital IT and lack of mobile solutions, so that records were completed on paper first and then transcribed to databases. Systems designed specifically for pandemic research should consider how data can be directly captured from patient monitors (eg, oxygen saturations and heart rate), and should look at more timely and efficient trial monitoring.

### Transparency of oversight

Finally, there was very strong feedback about the drug selection process for COVID-19 trials. Many respondents identified that this needed to be transparent, with clear routes of referral of drugs into the platform studies. An open drug selection process, with explicit criteria for drug selection at each phase, that investigators can trust, is vital for clinicians to coalesce efforts around a national platform approach.

### Limitations

Limitations of this survey include a response skewed towards PIs. The survey was cascaded from academic leads through their institutions and therefore predominantly reflects experience in large teaching hospitals, which may not be universally applicable. All respondents were from the UK, and some of the issues identified relate to specific UK approaches to the pandemic. There is, however, still important learning to be gained that is applicable to other jurisdictions. As with any thematic review, the experience of the authors, while essential to contextualise answers, may inadvertently lead to unconscious bias in coding and analysing data. To counterbalance this the authors have been careful to ensure that non-PI and clinician voices are represented within the thematic analysis.

### CONCLUSIONS

This thematic review reflects on the experiences of developing and delivering a research response to a rapidly

emergent pandemic respiratory infection. The focus of the review was on delivering large scale clinical trials, the remit of the R-TRC, but the experiences described and the recommendations made have much broader application to clinical trials in general. Alongside considerable triumphs, there were also aspects of the research response to COVID-19 where improvements could be identified. Key themes that have emerged include establishing a national infrastructure to actively advance early phase pandemic drug trials, that is seamless between phase 2 and 3, and which includes strands that allow rapid examination of the scientific rationale of drugs. This framework should be inextricably linked to regulatory assessment both at national and local levels, and delivered through a collaborative network of sites with pre-agreed contracts and material transfer agreements. Studies need designed for the realities of acute pandemic care and intended for delivery by a wide range of staff. Study processes should be tested to ensure they achieve this. Advance work can be done now to capitalise on innovative use of information technology to simplify process of informed consent for patients and researchers. The COVID-19 pandemic has exacted a high toll on patients and healthcare professionals. We hope that the learning we have gained from this pandemic, presented here, can be used to help us better prepare to face future similar challenges.

#### Author affiliations

<sup>1</sup>Division of Infection, Immunity and Respiratory Medicine, The University of Manchester Faculty of Medical and Human Sciences, Manchester, UK

<sup>2</sup>Division of Diabetes, Endocrinology and Gastroenterology, The University of Manchester Faculty of Biology Medicine and Health, Manchester, UK

<sup>3</sup>Department of Respiratory Medicine, Salford Royal NHS Foundation Trust, Salford, UK

<sup>4</sup>Institute of Continuing Education, University of Cambridge, Cambridge, UK

<sup>5</sup>Department of Paediatrics, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK

<sup>6</sup>National Heart & Lung Institute, Imperial College London, London, UK

<sup>7</sup>School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton School of Medicine, Southampton, UK

<sup>8</sup>Centre of Infection and Immunity, Queen's University Belfast, Belfast, UK

<sup>9</sup>Manchester Centre for Infection and Inflammation Research, The University of Manchester Faculty of Biology Medicine and Health, Manchester, UK

<sup>10</sup>Cambridge Institute for Medical Research, University of Cambridge, Cambridge, UK

<sup>11</sup>Royal Papworth Hospital NHS Foundation Trust, Cambridge, UK

<sup>12</sup>Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, UK

<sup>13</sup>Centre for Inflammation & Tissue Repair, University College London Division of Medicine, London, UK

<sup>14</sup>Interstitial Lung Disease Service, University College London Hospitals NHS Foundation Trust, London, UK

<sup>15</sup>Clinical and Experimental Medicine, University of Southampton School of Medicine, Southampton, UK

<sup>16</sup>Institute of Lung Health, University of Leicester, Leicester, UK

<sup>17</sup>MRC Human Immunology Unit, Weatherall Institute of Molecular Medicine, Oxford, UK

<sup>18</sup>Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford, UK

**Twitter** Alex R Horsley @alexrhorsley

**Contributors** ARH and L-PH conceived the study. ARH, L-PH, LP and SK developed the questionnaire which was also reviewed and refined by JD, RD, LGH, TH, SJM, LPM, JP, TW and CB. All authors were involved in questionnaire dissemination. ARH, LP, SK, NS, RW, MB and RCR conducted analysis and thematic review. All authors

contributed to final thematic discussion and manuscript. AH acts as guarantor for the study, accepts full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish

**Funding** This study received no specific funding but was led by the National Institute for Health Research (NIHR) Respiratory Translational Research Collaboration (R-TRC). The R-TRC is supported by the NIHR Respiratory Biomedical Research Centres of Cambridge, Guys and St Thomas (London), Imperial College (London), Leicester, Manchester, Nottingham, Oxford, and Southampton Universities, University College London, and the Northern Ireland Clinical Research Facility in Belfast.

**Competing interests** ARH, JD, RD, LGH, TH, SJM, LPM, JP, TW, CEB and LPH are all supported by their respective NIHR Respiratory Biomedical Research Centres. Separate to this work: ARH reports grants from JP Moulton Charity, CF Trust, CF Foundation, MRC and UKRI and personal fees from Vertex Pharmaceuticals and Mylan Pharmaceuticals. JD reports grants from CF Trust, CF Foundation, CF Ireland, EPSRC and personal fees Vertex Pharmaceuticals, Boehringer-Ingelheim, Elox, Aligpharma, Abbvie, Arcturus, Enterprise Therapeutics. RD reports grants from ERS, Teva, GSK, Novartis, Sanofi, Chiesi and personal fees from Synairgen, Sanofi-Genzyme, Galapagos, GSK, AstraZeneca and Airways Vista, and personal shares in Synairgen. LGH reports grants from MRC, including with multiple industrial partners, and personal fees from Astra Zeneca, Novartis, Roche/Genentech, GlaxoSmithKline, Chiesi, Teva, Theravance and Vectura. SM reports grants from BLF, MRC, June Hancock Mesothelioma Research, Alpha-1 Foundation, and Myrolitis Trust. JP reports grants from UKRI, LifeArc and MRC. TW reports grants from UKRI, Synairgen, AZ, UCB, Bergenbio and personal fees from Synairgen and Valneva. CEB reports fees to his institution from AZ, GSK, Novartis, Chiesi, BI, Genentech, Roche, Sanofi, Regeneron, Mologics, 4DPharma, Synairgen, Merck.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request. Anonymised data are available on request.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iDs

Alex R Horsley <http://orcid.org/0000-0003-1828-0058>

Stefan J Marciniak <http://orcid.org/0000-0001-8472-7183>

Chris Brightling <http://orcid.org/0000-0002-5803-5121>

#### REFERENCES

- 1 Guan WJ, ZY N, Hu Y. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020.
- 2 Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
- 3 Organisation WH. Timeline of WHO's response to COVID-19, 2020. Available: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline#>
- 4 Lillie PJ, Samson A, Li A, *et al*. Novel coronavirus disease (Covid-19): the first two patients in the UK with person to person transmission. *J Infect* 2020;80:578–606.
- 5 Angus DC, Berry S, Lewis RJ, *et al*. The REMAP-CAP (randomized embedded multifactorial adaptive platform for community-acquired pneumonia) study. rationale and design. *Ann Am Thorac Soc* 2020;17:879–91.
- 6 Docherty AB, Harrison EM, Green CA, *et al*. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical



- Characterisation Protocol: prospective observational cohort study. *BMJ* 2020;369:m1985.
- 7 Collins S, Self W, Mebazza A. Lessons from COVID-19 for acute care research in a Post-Pandemic world. *Lancet Respiratory Medicine* 2022.
  - 8 Braun V, Clarke V, Boulton E. The online survey as a qualitative research tool. *International Journal of Social Research Methodology* 2020;1–14.
  - 9 Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;3:77–101.
  - 10 O'Brien BC, Harris IB, Beckman TJ, *et al*. Standards for reporting qualitative research: a synthesis of recommendations. *Acad Med* 2014;89:1245–51.
  - 11 LaDonna KA, Taylor T, Lingard L. Why open-ended survey questions are unlikely to support rigorous qualitative insights. *Acad Med* 2018;93:347–9.
  - 12 RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (recovery): a randomised, controlled, open-label, platform trial. *Lancet* 2020;396:1345–52.
  - 13 RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (recovery): a randomised, controlled, open-label, platform trial. *Lancet* 2021;397:1637–45.
  - 14 RECOVERY Collaborative Group, Horby P, Lim WS, *et al*. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021;384:693–704.
  - 15 RECOVERY Collaborative Group, Horby P, Mafham M, *et al*. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med* 2020;383:2030–40.
  - 16 Wilkinson T, Dixon R, Page C, *et al*. Accord: a multicentre, seamless, phase 2 adaptive randomisation platform study to assess the efficacy and safety of multiple candidate agents for the treatment of COVID-19 in hospitalised patients: a structured summary of a study protocol for a randomised controlled trial. *Trials* 2020;21:691.
  - 17 Fisher BA, Veenith T, Slade D, *et al*. Namilumab or infliximab compared with standard of care in hospitalised patients with COVID-19 (catalyst): a randomised, multicentre, multi-arm, multistage, open-label, adaptive, phase 2, proof-of-concept trial. *Lancet Respir Med* 2022;10:255–66.
  - 18 Monk PD, Marsden RJ, Tear VJ, *et al*. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Respir Med* 2021;9:196–206.
  - 19 Lu IN, Kulkarni S, Fisk M, *et al*. muLTi-Arm therapeutic study in pre-ICU patients admitted with Covid-19-Experimental drugs and mechanisms (TACTIC-E): a structured summary of a study protocol for a randomized controlled trial. *Trials* 2020;21:690.
  - 20 Health and Social Care aSaTC. *Coronavirus: lessons learned to date*. London: House of Commons, 2021.
  - 21 van der Plas JL, van Esdonk MJ, Kamerling IMC, *et al*. Accelerating vaccine trial conduct in a pandemic with a hot spot-based inclusion strategy using trial and epidemic simulation. *Clin Transl Sci* 2021;14:2391–8.
  - 22 RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (recovery): a randomised, controlled, open-label, platform trial. *Lancet* 2022;399:2021.06.15.21258542.
  - 23 Pessoa-Amorim G, Campbell M, Fletcher L, *et al*. Making trials part of good clinical care: lessons from the recovery trial. *Future Healthc J* 2021;8:e243–50.

Large scale clinical trials - lessons from the COVID-19 pandemic.

## Supplementary data

### 1. Survey

The text of the survey is reproduced below.

#### Introduction

Thank you for completing this questionnaire. This survey reviews the experiences of planning, set up and delivery of experimental medicine and early phase therapeutic trials during the first year of the COVID-19 pandemic. The survey is disseminated via the R-TRC academic leads. It aims to understand the challenges faced, lessons learnt and also approaches adopted that were deemed helpful and successful. Responses are mainly free text.

#### About you

Please note - You will be given the option to leave your contact details at the end if you wish, but this is not obligatory

A. How would you describe your role? Please tick all that apply

- Principal Investigator
- Chief Investigator/Platform Lead
- Consultant
- Registrar
- Other physician
- Basic scientist
- Clinician scientist
- Early researcher
- Research administrator
- Research Nurse
- Research pharmacist
- Other:

B. What role(s) did you play in COVID19 response? Tick all that apply

- Study design and conception
- Study Investigator
- Recruiting and consenting patients
- Managing patients in trials
- Study admin
- Other:

C. What studies were you involved with? Please tick all that apply

- RECOVERY
- ACCORD
- TACTIC
- CATALYST
- DEFINE
- AGILE
- Other

#### 1. Design of studies\*, and impact of study design on delivery

This concerns any aspects of study design that impact, positively or negatively, on ability to deliver in a pandemic. \*\*Studies' refers throughout this survey to clinical trials or any relevant research studies

COVID research experience is divided into different domains. It is not expected that respondents will have experience of all domains, so please only answer where you feel you can.

- No experience in this domain (proceed to next section)

1.1 Please record your impressions of what aspects of study design worked well in the pandemic?  
(Free text response)

Large scale clinical trials - lessons from the COVID-19 pandemic.

*1.2 What aspects of study design were less effective in the context of the pandemic?*

(Free text response)

*1.3 What recommendations would you make with respect to study design?*

(Free text response)

## **2. Challenges in trial and study set up**

This concerns any aspect of set-up or administration that impacted on ability to deliver research in a timely manner

No experience in this domain (proceed to next section)

*2.1 Please record your impressions of what aspects of study set-up worked well in the pandemic?*

*2.2 What aspects of study set-up were less effective in the context of the pandemic?*

*2.3 What recommendations would you make with respect to study set-up?*

## **3. Study delivery**

This can include anything at a national, local or practical level that impacted on ability to deliver research in a timely and effective manner.

No experience in this domain (proceed to next section)

*3.1 Please record your impressions of what aspects of study delivery worked well in the pandemic?*

*3.2 What aspects of study delivery were less effective in the context of the pandemic?*

*3.3 What recommendations would you make with respect to study delivery?*

## **4. Patient engagement and consent**

This relates to any part of the engagement or consent process that impacted on ability to deliver research in a pandemic

No experience in this domain (proceed to next section)

*4.1 Please record your impressions of what aspects of patient engagement and consent worked well in the pandemic?*

*4.2 What aspects of patient engagement and consent were less effective in the context of the pandemic?*

*4.3 What recommendations would you make with respect to patient engagement and consent?*

## **5. Trials and study regulation, environment and organisation**

This relates to any aspect of the trials environment and regulation that impacted on ability to deliver timely and effective research.

No experience in this domain (proceed to next section)

*5.1 Please record your impressions of what aspects of the trials and study environment worked well in the pandemic?*

*5.2 What aspects of the trials and study environment were less effective in the context of the pandemic?*

*5.3 What recommendations would you make with respect to future set up of the trials and study environment*

## **6. National strategies and communication**

Large scale clinical trials - lessons from the COVID-19 pandemic.

This refers to how national strategies and the way trials were communicated to the public impacted on ability to deliver research.

- No experience in this domain (proceed to next section)

*6.1 Please record your impressions of what aspects of the national strategies and communication worked well in the pandemic?*

*6.2 What aspects of the national strategies and communication were less effective in the context of the pandemic?*

*6.3 What recommendations would you make with respect to the national strategies and communication?*

## **7. Other issues**

Please record any other observations or thoughts on research delivery and how to improve this in a pandemic

- No experience in this domain (proceed to next section)

*7.1 Please record here any other aspects of good or successful practice in pandemic trials and research studies*

*7.2 Please record here any other challenges you identified in successful pandemic trials and research studies.*

*7.3 Do you have any other comments about how you might plan or deliver things differently, if you had your time again?*

## **D. Optional contact details**

The following section is optional, but helpful for us if we need to contact you to discuss issues raised in more detail. In particular it would be helpful to know which centre you have experience of, so that we can ensure we have appropriate representation across the TRC.

- *Name*
- *Institution* (NB even if you don't provide your name this is helpful to ensure we get representative national coverage)
- *Would you be happy to be contacted to discuss any of the above in more detail? Yes/No*

Thank you for taking the time to complete this

Large scale clinical trials - lessons from the COVID-19 pandemic.

## 2. Study team reflexivity

LPH is the Chair of the R-TRC, and Professor of Respiratory Immunology at University of Oxford. Her expertise is in immune mechanisms in lung injury and repair, and she is an active clinician, specialising in interstitial lung diseases. She was a member of UPH, UK-CTAP, CRF and BRC Directors' COVID group, and on the steering or scientific advisory boards for ACCORD, CATALYST and AGILE. She has >20 years of clinical trial, clinical and basic science research experience. She led the development and conclusion of the survey with AH.

AH is Deputy Chair of the R-TRC, Professor of Respiratory Medicine at Manchester University, a specialist in adult Cystic Fibrosis, and a Director of the NIHR Manchester Clinical Research Facility. He has extensive experience in clinical trials pre-pandemic at all phases. During the pandemic AH was a PI for the ACCORD platform trial, the PHOSP-COVID study, the ESCAPE (1) and SIREN studies, and an investigator on the Synairgen(2), Theravance and RECOVERY trials. AH led the survey development and overall analysis of survey data.

LP, SK, MB, RW and RCR are Respiratory Specialist Trainees and hold various academic clinician and clinician scientist roles between them. All interpreted and coded data in specific sections of surveys. During the first wave of the pandemic, they were seconded back to clinical practice and were also involved in recruiting to trials. LP and SK set up clinical sampling to run in parallel to clinical trials and have extensive experience of data collection, interpretation and analysis across a number of COVID-19 studies (3-5). LP led a multi-centre clinical observational study of COVID-19 CPAP treatment efficacy.(6) SK has additional experience in COVID-19 study ethics (non-UPH badged). LP and SK developed themes with AH.

NS is a Consultant Paediatrician with experience in qualitative research methodologies, based at Cambridge University. NS is outside of the R-TRC structure, and separate from adult COVID-19 medicine and research, and has provided independent and objective input on methodology, analysis techniques and study findings.

Large scale clinical trials - lessons from the COVID-19 pandemic.

**3. Details of study respondents**

	Clinical academics/ clinicians n=50	Research nurses and pharmacists n=16	Research administration and management n=12	Others n=5	Total n=83
<b>BRC centres, n (%)</b>					
Cambridge University	6 (12%)	0	0	0	6 (7%)
Imperial College London	1 (2%)	0	0	1 (20%)	2 (2%)
Leicester University	2 (4%)	0	1 (8%)	2 (40%)	5 (6%)
Manchester University	4 (8%)	4 (25%)	0	1 (20%)	9 (11%)
Nottingham University	1 (2%)	0	0	0	1 (1%)
Oxford University	5 (10%)	3 (19%)	3 (25%)	0	11 (13%)
Queen's University Belfast	2 (4%)	0	1 (8%)	0	3 (4%)
Southampton University	2 (4%)	0	0	0	2 (2%)
University College London	4 (8%)	2 (13%)	0	0	6 (7%)
Birmingham*	1 (2%)	0	0	0	1 (1%)
Unknown	22 (44%)	7 (44%)	7 (58%)	1 (20%)	37 (45%)
<b>Roles in COVID-19 research, n (%)</b>					
Study investigator	36 (72%)	0	0	1 (20%)	37 (45%)
Study design and conception	24 (48%)	2 (13%)	1 (8%)	1 (20%)	28 (34%)
Recruitment and consenting	41 (82%)	8 (50%)	1 (8%)	1 (20%)	51 (61%)
Patient management	32 (64%)	10 (63%)	1	3 (60%)	46 (55%)
Administration	11 (22%)	5 (31%)	9 (75%)	4 (80%)	29 (35%)
Trial management	0	6 (38%)	4 (33%)	0	10 (12%)
Other	1 (2.0%)	1(17%)	1 (8%)	2 (40%)	5 (6%)
<b>Trials involved, n (%)</b>					
RECOVERY	35 (70%)	11 (69%)	5 (42%)	1 (20%)	52 (63%)
ACCORD	14 (28%)	5 (31%)	4 (33%)	1 (20%)	24 (29%)

## Large scale clinical trials - lessons from the COVID-19 pandemic.

CATALYST	7 (14%)	4 (25%)	2 (17%)	0	13 (16%)
COVID Vaccine trials	2 (4%)	3 (19%)	1 (8%)	0	6 (7.2%)
Synaigen	5 (10%)	4 (25%)	1 (8%)	0	10 (12%)
Theravance	1 (2%)	1 (6%)	0	1 (20%)	3 (3.6%)
PHOSP-COVID	4 (8%)	2 (13%)	2 (17%)	2 (40%)	10 (12%)
ISARIC	1 (4%)	1 (6%)	1 (8%)	3 (60%)	6 (7%)
Remdesivir	4 (8%)	4 (25%)	1 (8%)	0	9 (11%)
REMAP-CAP	2 (4%)	3 (19%)	2 (17%)	0	7 (8%)
ESCAPE	1 (2%)	1 (6%)	0	0	2 (2%)
Other trials	26 (52%)	8 (50%)	6 (50%)	3 (60.2%)	43 (52%)

**Supplementary table 1:** Survey respondents, including role, experience and affiliated research centre.

\*Birmingham was affiliated with Oxford BRC.

## References

1. Zuo J, Dowell AC, Pearce H, Verma K, Long HM, Begum J, et al. Robust SARS-CoV-2-specific T cell immunity is maintained at 6 months following primary infection. *Nat Immunol.* 2021;22(5):620-6.
2. Monk PD, Marsden RJ, Tear VJ, Brookes J, Batten TN, Mankowski M, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Respir Med.* 2021;9(2):196-206.
3. Mann ER, Menon M, Knight SB, Konkel JE, Jagger C, Shaw TN, et al. Longitudinal immune profiling reveals key myeloid signatures associated with COVID-19. *Sci Immunol.* 2020;5(51).
4. Shuwa HA, Shaw TN, Knight SB, Wemyss K, McClure FA, Pearmain L, et al. Alterations in T and B cell function persist in convalescent COVID-19 patients. *Med (N Y).* 2021;2(6):720-35 e4.
5. Scott NA, Knight SB, Pearmain L, Brand O, Morgan DJ, Jagger C, et al. Recovery of monocyte exhaustion is associated with resolution of lung injury in COVID-19 convalescence. *medRxiv.* 2020:2020.10.10.20207449.
6. Bradley P, Wilson J, Taylor R, Nixon J, Redfern J, Whittemore P, et al. Conventional oxygen therapy versus CPAP as a ceiling of care in ward-based patients with COVID-19: a multi-centre cohort evaluation. *EClinicalMedicine.* 2021:101122.