

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

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## 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.

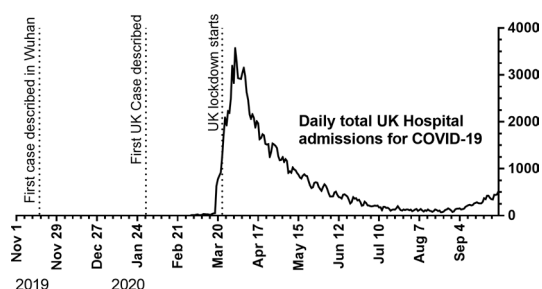
on 30 January 2020, the same date that the WHO declared a public health emergency. Infection within the UK had become widespread by March 2020.<sup>3,4</sup> The rapid spread of SARS-CoV2 caused widespread disruption across society and healthcare, and left little time for planning and design of research 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.



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**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

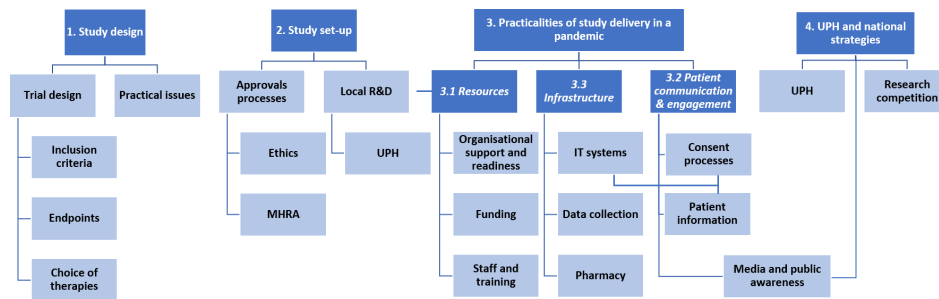
A reflexive, inductive, thematic analysis approach was employed, following the Braun and Clarke six-step approach to code and construct themes<sup>9</sup> and reported in line with the Standards for Qualitative Research.<sup>10</sup> Each section was independently reviewed by two reviewers who familiarised 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.

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**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

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

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