Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

during the current pandemic. Nonetheless, scientific knowledge and public health strategies must continue to evolve. Alternative vaccine platforms, vaccine doses, or vaccine schedules could reduce the risk of rare adverse events and must be explored in the context of changing infection risk.[10] Vaccine confidence is one our most valuable resources, and it is dependent upon trust in public health. Trust is a fragile commodity that is strengthened by reporting challenges transparently and addressing these challenges with scientific rigour and appropriate concern.

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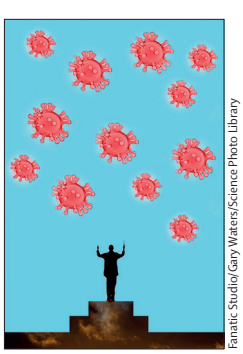
Early-phase clinical trials in a pandemic: learning from the response to COVID-19

The first cases of the novel SARS-CoV-2 virus emerged at the end of 2019 in Wuhan, China. Within 2 months, WHO had declared a public health emergency and the first cases were detected in the UK. The rapid spread of SARS-CoV-2 caused widespread disruption across society and health care, and left little time to plan and design research needed in the context of a new pandemic. Some studies (eg, ISARIC and REMAP-CAP) had pre-existing protocols that were rapidly adjusted, but in most instances, new research studies and clinical trials had to be set up rapidly to respond to the unique environment and challenges created by COVID-19. The success or otherwise of the adaptations made as part of this research response has been highly informative and provides an opportunity to plan effectively for future threats.

The UK adopted a streamlined approach to the delivery of vaccines and therapeutics, capitalising on a single National Health Service (NHS) and the UK National Institute for Health and Care Research (NIHR), a government-funded health research system linked to the NHS. The NIHR Respiratory Translational Research Collaboration (R-TRC) network was in a unique position to coordinate, set up, and conduct early-phase (typically phase 1 and phase 2) clinical trials required to test repurposed or unlicensed drugs for a new disease. Before the pandemic, the R-TRC's main objective was to accelerate delivery of new respiratory drugs via collaborative UK-wide efforts in partnership with industry. In the first few weeks of the pandemic, the R-TRC pivoted to work on mechanistic human immunology studies and phase 2 clinical trials of therapeutics across our ten major teaching hospitals and universities members. We supported one of the first immunology studies on COVID-19 in the UK[1] and used nascent scientific findings to help to select repurposed drugs for early-phase therapeutic trials. Ultimately, the R-TRC helped to deliver 15 phase 2 trials and two large, national phase 2 platform trials,[2,3] and contributed to drug selection via the national centralised UK COVID-19 Therapeutic Advisory Panel process.[4] Here, we discuss our experiences and lessons learned from the first year of the pandemic in the UK[5] and present recommendations for future planning of early-phase clinical trials during a pandemic.



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For more on **REMAP-CAP** https://www.remapcap.org/

For more on **RECOVERY** see https://www.recoverytrial.net/

For more on the **R-TRC** see https://www.nihr.ac.uk/partners-and-industry/industry/collaborate-with-us/respiratory-trc.htm

Panel: **Recommendations for clinical trials in future pandemics from the NIHR R-TRC network**

Recommendations for research infrastructure

- Integrate early-phase trials seamlessly with late-phase trials, and prioritise resources, patient recruitment, and regulatory examination for both trial types
- Design, set up, and test pandemic-response early-phase and late-phase clinical trials in advance
- Match central (national) organisation with local (eg, individual NHS trusts or Biomedical Research Centres) organisation and enhance local research and development capabilities to meet central requirements
- Employ national prioritisation processes that are transparent, responsive to researcher suggestions or concerns, and carefully communicated by a dedicated team
- Establish centres for translational research delivery and experimental medicine, where resources can be prioritised for more complex early-phase trials during a national emergency

Recommendations for early-phase clinical trials

- As far as possible, keep studies simple and pragmatic, designed for delivery in an acute environment
- Involve patient-facing clinicians, allied health professionals, and patients in the development of protocols, patient information, and consent methods
- Ensure that research clinicians maintain some protected time to use their experience and expertise to lead and run clinical trials
- Maximise use of innovative digital technology approaches for study set up and informed consent processes
- Make information sheets as short as possible, easy to follow, and available in multiple languages; complement information sheets with other forms of digital information
- Develop and test effective electronic data-capture systems that can work on existing information technology networks or portable data-capture tablets

NHS=National Health Service. NIHR=National Institute for Health and Care Research. R-TRC=Respiratory Translational Research Collaboration.

As discussed by Jonathan Casey and colleagues in *The Lancet Respiratory Medicine*,[6] it is indisputable that pragmatic trials (such as RECOVERY), which are embedded within routine clinical practice and are typically late-phase trials, have been vital for the rapid provision of new therapeutic drugs for COVID-19. We enthusiastically endorse the innovative methods that were used in the RECOVERY trial to engage clinicians, patients, and the public. The coordination of the clinical trial landscape by the NIHR via prioritisation of regulatory assessment, resources (mainly in the form of a national network of research nurses), and studies was an important factor in the success of RECOVERY, and highlights the transformative power of a national strategy. This coordination, however, evolved over a few months. There was an initial lack of expertise-focused leadership or mandate from the UK government during a very rapidly moving national emergency, reflecting the lack of preparedness for such a crisis. In particular, early-phase trialists and experimental medicine experts were under-represented in decision-making groups, providing grounds for these experts to start independent studies, which eventually led to parallel or duplicate studies in some cases.

A crucial acknowledgment of the need for early-phase trials was not apparent and was not even mentioned in the UK government's review of lessons learned from COVID-19.[7] Casey and colleagues[6] elegantly describe the value of early-phase trials (and use of what they refer to as explanatory designs) and large, pragmatic late-phase trials. Pragmatic trials are ideal for evaluating drugs already embedded in clinical practice. However, pragmatic designs are not suited to the study of new, unlicensed drugs, which require a greater level of informed consent, increased collection of safety information, and exploration of potential mechanistic implications. Findings from early-phase trials can reduce the odds of a negative result in phase 3 trials, integrate scientific questions and learning (particularly important for an unknown disease), delineate unexpected safety issues (especially with less well established drugs), and inform the selection of endpoints, including both biological and clinical outcomes. Phase 3 trials are costly in terms of patient numbers. Prioritisation of late-phase over early-phase COVID-19 trials resulted in competition for resources and patients. For example, to date, RECOVERY has recruited more than 46 000 patients, possibly at the expense of recruitment for phase 2 trials, leading to delays in the reporting of results from these smaller trials. The reality is that both types of trial are needed and provide vital complementary approaches to tackling lethal new diseases.

However, lessons from pragmatic trials could be applied to early-phase trials in future pandemics. Administration-heavy traditional trial methods, typically used by contract research organisations, are almost unworkable for the speed required to deliver results in a timely manner during a pandemic. Studies that are designed to interrupt clinical care as little as possible are crucial but, as highlighted by Casey and colleagues, explanatory approaches require greater resources for the more rigorous patient selection, informed consent processes, and follow-up.[6] Innovations in digital technologies have the potential to greatly enhance efficiency of trial information collection and consent processes, and are well suited to a pandemic environment, but their potential remains barely explored.

There now exists an opportunity to work with regulators and patient groups to review how much information is required for informed consent in these circumstances and to develop digital technology innovations, such as video explanations, to increase efficiency and maximise access to trials for all parts of society.

Large-scale trials require individual researchers to sacrifice a degree of scientific autonomy for the ultimate benefit of all. This requires careful communication to engender trust and exchange of information, and a high level of transparency. We observed that poor communication in the first few months of the pandemic regarding how studies were prioritised and how drugs were selected led to substantial mistrust and dissatisfaction among researchers and clinical trialists, and a consequent proliferation of smaller studies. There was also a lack of recognition of different capabilities across different hospital sites and scientific institutions. Clearly, some centres can do more complex trials or studies, whereas others are better at organising high levels of recruitment. Advance planning should recognise these differences and use the opportunity to optimise the strengths of different organisations.

It was also clear that multicentre human scientific studies to better understand mechanisms of disease should be prioritised at pace with clinical trials. Regulatory and contractual processes need to be simplified for an effective pandemic response: an often-cited issue during the early stages of the COVID-19 pandemic was protracted sign-off for material transfer agreements and other contracts between universities, which hampered sharing of clinical samples.

We conclude that there is a clear need for effective pandemic response preparation, well in advance of the threat. An integrated pathway from early-phase studies through to larger pragmatic trials will create confidence and engagement for both researchers and patients. We present key recommendations for research infrastructure and early-phase clinical trials that would be needed to ensure a timely response to the challenges of a future pandemic (panel). Ultimately, the worst outcome from the COVID-19 pandemic would be to go into the next pandemic no better prepared than we were when SARS-CoV-2 emerged.

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