Early phase clinical trials during COVID-19 - lessons for the next pandemic

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The first cases of the novel beta-coronavirus SARS Coronavirus 2 (SARS-CoV2) emerged at the end of 2019 in Wuhan, China[1]. Within two months, the World Health Organisation had declared a public health emergency and the first cases were detected in UK [1,2]. 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. Some studies (e.g. ISARIC, REMAP-CAP)[3,4] had pre-existing protocols that were rapidly adjusted, but in most instances COVID-19 research studies and clinical trials had to rapidly adapt to the unique environment and challenges created by the pandemic. The success or otherwise of these adaptations 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 Health Institute of Research (NIHR), a government funded health research system linked to the NHS. The NIHR's Respiratory Translational Research Collaboration (R-TRC) network[5] was in a unique position to coordinate, set up and conduct early phase, so called phase 2, clinical/ therapeutic trials (sometimes referred to as 'explanatory trials'). Pre-pandemic, the R-TRC's main objectives were 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 helping deliver mechanistic human immunology studies and phase 2 therapeutic trials across our ten major teaching hospitals and universities members. We supported one of the first immunology studies on COVID-19 in UK[6] and utilised nascent scientific findings to help select repurposed drugs for early phase therapeutic trials. Ultimately, the R-TRC helped deliver 15 early phase trials and two large national phase 2 platform trials[7,8], contributed to advise on drug selection via the national centralised UK-Coronavirus Therapeutic Advisory Panel (CTAP) process[9], and helped link central decision-makers to delivery teams. Here we discuss our experiences and learning from the first year of the pandemic, and our recommendations for future planning.

It is indisputable that pragmatic trials like RECOVERY have been vital to the rapid delivery of new therapeutic drugs to patients, and we enthusiastically endorse the innovative methods 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 national network of research nurses) and studies were important factors for the success of RECOVERY, and highlight the transformative power of a national strategy. This coordination, however, evolved over a few months. There was an initial vacuum of expertise-focused leadership or mandate from the government of 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, providing grounds for these experts to take individual leads and make individual investments in funds, time and effort which eventually led to parallel or duplicated studies in some cases.

A critical acknowledgement of the need for early phase trials was not apparent, and was not even mentioned in the UK government's lessons learnt review.[9] Collins et al[10] describe the utility of early (or explanatory) and late (pragmatic in the case of RECOVERY) trials elegantly: pragmatic trials are ideal for evaluating re-purposed drugs, and particularly those already embedded in clinical practice. But they are not suited for new, unlicensed drugs where a greater level of informed consent is required, and greater effort is needed to collect safety information and explore potential mechanistic implications. Early phase trial can spread or reduce the odds of a negative result, integrate scientific questions and learning (particularly important in an unknown disease), delineate unexpected safety issues, especially with less well-established drugs, and help devise end points that include both biological and clinical outcomes. Another 'cost' of phase 3 trials are patient numbers. Prioritization of late phase trials without equal priority for early phase trials resulted in competition for patients and resource, and delay in reporting for phase 2 trials. To date, RECOVERY has recruited >46,000 patients to deliver three drugs to clinical practice. Many researchers point to competition for patients at recruitment sites and the large number required by RECOVERY, at the expense of smaller phase 2 trials. The reality is that both are needed and provide vital complementary approaches to tackling lethal infectious threats.

Early or phase 2 trials however can take many leaves from the book of pragmatic trials for future pandemics. For a rapid deployment, administration-heavy traditional trial methods typically used by contract research organisations (CRO) are almost unworkable for the speed required to deliver results in a timely fashion. Studies that are designed to interrupt clinical care as little as possible are crucial, but as Collins et al highlight greater resources are still required for the more rigorous follow-up, informed consent and patient selection[10]. Innovations in digital technologies for example have the potential to greatly enhance efficiency of trial information and consent processes, and are well suited to work in a pandemic environment, but the potential remains barely explored. There exists now 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 IT innovations, for example video explanation, to increase efficiency and maximise access to trials for all parts of the society.

Large scale trials request individual researchers to yield a degree of autonomy of scientific freedom 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 of how studies were prioritised and how drugs were selected in the first few months of the pandemic led to significant mistrust and dissatisfaction, and a consequent proliferation of smaller studies. There was also a lack of recognition of different capabilities across different hospital sites and scientific institutions and acceptance that some centres can do more complex trials/studies, while others are better at organising high levels of recruitment. Advance planning should recognise this and optimise the opportunity to utilise the strengths of different organisations.

Finally, it was also clear that multi-site human scientific studies should be prioritised at pace with clinical trials. Regulatory and contractual processes need to be simplified for effective pandemic response: an oft-cited issue was protracted sign-off for Material Transfer Agreements and other contracts between Universities which hampered sharing of clinical samples.

We conclude that there was clear need for effective pandemic response preparation, well in advance of the threat. Prior 'hibernating' approvals for integrated phase 2/3 trials and data, and practical matters such as training packages can all be prepared, ready for dissemination digitally. Multiple simultaneous studies created pressures for staff and patients, and an integrated pathway from early phase studies through to larger pragmatic trials will create confidence and engagement for researchers and patients alike. 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. We have condensed our key recommendations for infrastructure and trials for the next pandemic which we present in Table 1. Ultimately the worst outcome from this pandemic would be to enter the next pandemic with no better preparation than we faced this one.

	Infrastructure recommendations
1.	Early phase trials should be integrated seamlessly with late phase trials, and prioritisation in resource, patient recruitment and regulatory examination provided for both.
2.	Design, set up and test pandemic-response early and late phase clinical trials in advance.
3.	Match central (national) organisation with local (individual NHS Trust/BRC) organisation and enhance local Research and Development capabilities to meet central requirements
4.	National prioritisation processes need to be transparent, responsive to researcher suggestions/concerns and carefully communicated by a dedicated team
5.	Establish centres for translational research delivery and experimental medicine, where resources can be prioritised to more complex early phase trials during a national emergency.

	Clinical trial-specific recommendations for early phase trials in a pandemic
1.	As far as possible keep studies simple and pragmatic, designed for delivery in an acute environment.
2.	Involve patient-facing clinicians and allied health professionals, and patients in protocol development, acceptable patient information and consent methods
3.	Ensure research clinicians maintain some protected time to utilise their experience and expertise to lead and run clinical trials
4.	Maximise innovative use of information technology approaches to informed consent and study set up
5.	Make information sheets easy to follow and as short as possible, and complement with other forms of digital information. Make information sheets available in multiple languages.
6.	Develop and test effective electronic data-capture systems that can work on existing IT networks or portable data-capture tablets.

Table 1. Recommendations from the NIHR Respiratory-Translational Research Collaboration network for early phase trials for future pandemics

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