# Experience of conducting clinical trials of investigational medicinal products during a respiratory virus pandemic: Lessons learnt from COVID-19

Running Head: Conducting clinical trials during COVID-19

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The rapid spread of Severe Acute Respiratory Syndrome, Coronavirus-2 (SARS-CoV-2) caused a surge in research activity aimed at treatment and prevention interventions for coronavirus infectious disease 2019 (COVID-19). The global medical research community reacted quickly to initiate clinical trials testing novel and repurposed medicines as possible treatments. As of 5th October 2020, 56 randomised intervention studies have registered activity in the United Kingdom, the earliest in March 2020.[1] These efforts have already yielded advances in COVID-19 management.[2]

In the setting of a pandemic novel pathogen, a sudden increase in trial activity generated logistical challenges. These were compounded by: a large influx of cases saturating hospital capacity, staff isolation, sickness and redeployment, fear of infection, and demand on researchers to operationalise complex regulatory studies quickly.

Patients with COVID-19 received care in isolation wards with strict entry and exit procedures and prohibition of visitors. This can be a lonely experience, worsened by staff anonymity when wearing personal protective equipment. Patient fear is common during outbreaks of emergent pathogens[3] and may adversely affect their willingness to consider trial enrolment. Attempts to discuss trials were further impacted by factors including the noise associated with non-invasive ventilation. Effective communication is key and strategies should be utilised to reassure patients alongside giving them sufficient information to ensure informed consent, such as offering a joint telephone discussion with their family.

Maintaining infection control measures whilst obtaining informed consent in this environment required a flexible approach. The adapted operational strategy utilised is outlined in Figure 1. One wet signature signed copy was double-bagged prior to exiting a COVID-19 ward and quarantined with the site file for the minimal duration deemed necessary for the pathogen to become unviable (e.g. up to one week for SARS-CoV2).[4] Signed consent forms were digitally uploaded into medical records; the participant received a printed copy.

Prior to obtaining signed consent it is essential that potential participants receive sufficient information to make an informed decision. Lengthy participant information sheets and consent forms can generally be a barrier to recruitment, exacerbated in a pandemic due to the higher propensity for patients to be acutely unwell and have consent fatigue given they are often approached for multiple studies. One study found participant information sheets had an average length of 23 pages,[5] though participants can feel less informed when lengthy documents are used.[6] Condensing documents to essential information, whilst maintaining regulatory compliance would be particularly beneficial during a pandemic e.g. bulleted key messages and infographics. For individuals whose first language differs from the main language of the site, approved document translations are often not available, with limited access to face-to-face translators due to access restrictions and limited telephone availability within quarantine areas. In these circumstances, simplified video or audio-visual information approved for the consenting process may be advantageous. This could deliver information in multiple languages and to those too unwell to read text.[7]

A pandemic of a pathogen that can manifest with severe acute illness may cause many patients to be physically incapable of providing a wet signature, though still able to give informed consent. In this scenario, information can be summarised verbally and a witness can sign for the participant. The witness cannot be associated with the study and should observe the entire consenting consultation.[8] For patients with mental incapacity, a legal representative is required and should undergo the same consent procedures as if they were the patient.[8] Individuals eligible to be legal representatives or witnesses can vary by country or region. It is good practice to involve a next of kin when feasible; the clinical team should facilitate this to avoid confidentiality breaches. Due to visiting restrictions, we discussed trials with the next of kin via telephone and used a professional legal representative (e.g. the senior clinician overseeing the patient's care, if independent of the study team) to complete the consent form, which is valid procedure in the United Kingdom.[9] Figure 1 incorporates an algorithm outlining this process. Research teams should ensure they are familiar with local regulations.

Patients recognise the benefits of clinical trial enrolment during a pandemic.[10] However, they may be at risk of having unrealistic expectations of trial treatments and decisions may be made in haste.[11] Good clinical practice encourages allowing 24 hours for a potential participant to review study information;[8] this may not be feasible if time-to-treatment could affect outcomes. Investigators should be particularly vigilant during a pandemic to ensure that patients understand their options, address any therapeutic misconceptions, and ensure patients do not feel pressured to make a decision.[8]

Reflecting on participant experiences and incorporating patient and public involvement in future pandemic research planning and implementation may improve consent processes and trial follow up under these challenging conditions. This could also improve public acceptability and recruitment into studies during a pandemic.

The rapid spread of COVID-19 presented us with a unique combination of logistical challenges for the conduct of clinical trials, compounded by high demands on health services and the need to expedite implementation of multiple concurrent interventional studies. Clinical research teams played an essential part in delivering trials that are leading to improved outcomes for patients. The implementation of streamlined procedures by regulatory authorities have been invaluable in expediting study set-ups. Whilst broader guidelines currently exist,[3] there is scope for further methodological work to develop a generalisable operational toolkit that trial investigators can utilise. This should include input from sponsors and investigators on the challenges faced when delivering trials under pandemic conditions, incorporating the advice of patients and public stakeholders who have experienced participation in COVID-19 studies.

Clear procedures, such as those outlined, can help to overcome some of the barriers associated with infection control measures, the clinical status of patients, and the often complex consent processes. Innovative approaches to obtaining consent, including e-consent, and streamlined participant information could

help. The experience to date can be applied to the anticipated further waves of COVID-19, or to future outbreaks of infectious diseases, and more generally, to support development of simplified approaches to delivering randomised trials in an urgent public health setting.[12]

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**Conflict of Interest**

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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**Figure 1**. Example of undertaking an informed consent process in a quarantine area

*One PIS/ICF for wet signature can be used as an alternative. A digital copy can then be created on the ward for the participant copy. †Review local regulations to determine a suitable legal representative. ICF: informed consent form, PIS: patient information sheet, PPE: personal protective equipment.