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.

Clinical trials of disease stages in COVID 19: complicated and often misinterpreted

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As of July 28, 2020, 1840 clinical trials were registered globally, with 1001 clinical trials recruiting patients for COVID-19 management.[1] Despite this large number, only 30 trials have been published as peer-reviewed or preprint publications.[2] Media reports and prepublications on *medRxiv* and *bioRxiv* represent the most frequent mechanism for data sharing, with wide public reach and usually with little detail. However, with inadequate details on the trials and only superficial scrutiny by the public and scientific decision makers, the consequences have had disastrous effects on other clinical trial funding, permissions, recruitment, and interpretation.

Broadly, COVID-19 clinical trials target at least five stages of the disease process (appendix): pre-exposure prophylaxis, post-exposure prophylaxis, outpatient treatment, hospital admission, and late-stage critical care (admission to an intensive care unit). More clinical stages for COVID-19 arguably exist if looking at subgroup manifestations of COVID-19. Despite the overwhelmingly large number of trials being done for COVID-19, it is important to note that the majority of these trials (1134 [61·6%] of 1840) involve patients who have been admitted to hospital.

Among all clinical trials, those receiving the greatest media and scientific attention include the WHO SOLIDARITY trial (ISRCTN83971151) and the Randomised Evaluation of Covid Therapy trial (RECOVERY; ISRCTN50189673). Both of these randomised trials target patients receiving treatment in hospital and have proven the ineffectiveness of lopinavir–ritonavir[3] and hydroxychloroquine[4] for patients admitted to hospital with COVID-19. Although both trials provide convincing evidence for patients requiring hospital admission, these findings cannot be translated to other disease states. For example, in the RECOVERY trial, the clinical efficacy of low-dose dexamethasone is demonstrated only among patients receiving invasive mechanical ventilation or oxygen.[5] Clinical trials investigating treatment options in other disease states are experiencing unintended consequences of early dissemination of this inpatient evidence. Many trials evaluating chloroquine-based treatments and protease inhibitors for pre-exposure prophylaxis and outpatient treatment have had funding and ethics approvals rescinded based on media attention on findings from hospital settings. This misinterpretation of disease states exists among both the public and the scientific communities.

Different COVID-19 disease stages encompass different biological responses, and pharmaceutical interventions might exhibit different effects according to concurrent pathogenesis. The initial remdesivir randomised trial on patients receiving treatment in hospital, in which the median time to remdesivir initiation after symptom onset was 11 days, did not show important statistical benefits for time to clinical improvement.[6] A subsequent randomised trial that initiated remdesivir at a median of 9 days after symptom onset, by contrast, found a shorter recovery time in patients with less severe pulmonary disease than in the placebo group.[7] The findings support the likely efficacy of this antiviral early in disease when viral replication predominates. Conversely, the dexamethasone findings in the RECOVERY trial found benefit in patients with more severe disease requiring oxygen or respiratory support,[5] supporting an anti-inflammatory effect when inflammation pathology predominates. As seen for other viral infections such as influenza and varicella zoster, there is a need for early antiviral treatment for COVID-19 because antivirals are probably most effective when administered early in an infection, whereas systemic hyperinflammation rather than viral pathogenicity dominates later stages of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[8] Differentiation of effects based on an antiviral's mechanism of action is also anticipated with SARS-CoV-2, with interventions affecting viral attachment being more dependent on early initiation than therapeutics targeting other parts of the viral cell cycle.[9]

Although it is clear that some therapies have no clinical benefits in patients admitted to hospital, there is much uncertainty, and thus clinical equipoise, to justify continuing clinical trials in other COVID-19 disease states. Most ongoing trials are focusing on participants admitted to hospital, and generalising

See Online for appendix

their findings to ambulatory patients might potentially harm opportunities to identify effective outpatient treatments. Arguably, the largest impact on COVID-19 can be achieved by identifying effective early treatments to prevent hospital admission. Although we hope that scientific funders and ethics review boards will recognise the nuances of COVID-19 disease states, this has not been uniformly the case so far. Delaying or rescinding funding or approvals for clinical trials based on findings from clinically different populations might importantly reduce our likelihood of finding effective therapies across the spectrum of clinical disease states.

We declare no competing interests.

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