COVID-19 clinical trials: see it big and keep it simple

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly emerged as a major threat to healthcare systems across the globe, resulting in the launch of unprecedented containment efforts by governments worldwide. In many countries, quarantines and stay-at-home orders have been imposed in an attempt to flatten the epidemiological curve and mitigate the acute burden of COVID-19 on hospitals and clinics. Such measures may remain necessary until a safe and effective therapy or vaccine against the disease has been developed.

In response to the present pandemic, the US Food and Drug Administration and the European Medicines Agency (EMA) have set up programmes[1 2] to incentivise and expedite the development of COVID-19 treatments and vaccines. The International Coalition of Medicines Regulatory Authorities has stressed the importance of randomised controlled trials (RCTs) for generating the robust level I evidence required to support the uptake of promising therapeutic strategies into clinical practice.[3] Currently, more than 1000 interventional studies investigating over 400 different anti-SARS-CoV-2 drug candidates are being conducted.[4] However, the vast majority of these are small, single-country or even single-centre trials,[5–8] despite the fact that EMA has called for the pooling of resources into large, multiarm, multicentre, multicountry RCTs.[9] Although such limited-scale studies have their merits, their design often jeopardises their external validity and introduces uncertainty into the interpretation of their outcomes: who is to say that an intervention that works in one hospital in a particular country will also be beneficial when applied under different circumstances elsewhere?

To optimise the COVID-19 research response, we urge investigators to heed EMA's recommendations and partake in the so-called large simple trials (LSTs). LSTs are, as the name would suggest, pragmatically designed studies that enrol a large number of participants according to a relatively straightforward protocol.[10–12] Many different countries and institutions usually contribute to the recruitment process of LSTs. Due to the limited number of inclusion and exclusion criteria, the heterogeneous sample of trial subjects in an LST closely resembles the real-world patient population. The study procedures are embedded into routine clinical practice as much as possible so as to avoid additional organisational and administrative work. While blinding is typically absent in LSTs, randomisation remains a core methodological principle of these studies as it lowers the risk of biased outcomes. The endpoints of LSTs are hard, objectively measurable and of direct relevance (eg, death), as opposed to the surrogate endpoints that have become the standard in many trials today. From a statistical point of view, LSTs are capable of detecting even small treatment effects that are likely to carry over to a real-life, non-experimental setting.

The LST concept is not new: it was first outlined almost four decades ago.[13] Nevertheless, there has been a renewed stakeholder interest[10–12] in these studies in recent years as a result of the growing dominance of industry-sponsored trials, which have become increasingly complex and costly to perform.[14] In light of the current crisis, LSTs present an attractive approach for collecting data on the safety and efficacy of potential COVID-19 therapies and vaccines. Their inherent simplicity lowers the barrier to entry for the participating institutions and their large sample size strengthens the validity of their findings.[10–12] Additionally, as compared with smaller and more intricately devised RCTs, LSTs tend to be more cost efficient to undertake.[10–12] All of these aspects are appealing, especially when considering the financial and operational pressures our healthcare systems are facing and the urgent need for RCT-derived evidence to establish COVID-19 treatment guidelines.

The solidarity trial[15] initiated by the World Health Organization should serve as an example in this regard. This open-label randomised study, which has been rolled out in over 100 countries so far, was purposefully designed to be easily integrated into overburdened hospital settings. Participants receive the local standard of care alone or in combination with one of four experimental therapeutic regimens: lopinavir and ritonavir with or without interferon beta-1a, remdesivir, or (hydroxy)chloroquine. Data are only collected at the moment of randomisation and when the patient has either died or been discharged, reducing trial paperwork to a minimum. In addition, the distinct lack of selection criteria significantly facilitates the recruitment process: all adult patients with COVID-19 without contraindications to any of the investigational treatments are eligible for participation. Furthermore, the oversight of the study conduct by independent experts ensures that there are no commercial motives clouding the interpretation and reporting of the results. Once completed, the solidarity trial will provide clinicians with some of the strongest evidence yet to guide their decision-making relating to COVID-19 cases, likely at a fraction of the time and the cost it would have taken to set up multiple smaller scale studies of equal evidentiary value.

While undoubtedly having the best interests of COVID-19 patients at heart, both academic and

industry-affiliated scientists are racing to be the first to realise a research breakthrough and deliver the groundbreaking therapy or vaccine everybody has been waiting for, in large part because it will advance their own careers. However, we need to think bigger and adopt a more collaborative approach to anti-SARS-CoV-2 drug development. It is certainly true that competition fosters innovation, but we must remember that extraordinary times call for extraordinary measures. A pandemic with far-reaching social, economic and political consequences necessitates strong collaboration on all levels. If we want to find a way to prevent or treat COVID-19, our clinical research efforts need to be streamlined as much as possible. LSTs in particular are valuable tools through which promising drugs can be evaluated collectively and deserve more attention from clinicians in the field.

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