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.

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Short Communication

Moving forward in clinical research with master protocols

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A B S T R A C T

With billions of dollars in research and development (R&D) funding continuing to be invested, the novel coronavirus disease 2019 (COVID-19) has become into a singular focus for the scientific community. However, the collective response from the scientific communities have seen poor return on investment, particularly for therapeutic research for COVID-19, revealing the existing weaknesses and inefficiencies of the clinical trial enterprise. In this article, we argue for the importance of structural changes to existing research programs for clinical trials in light of the lessons learned from COVID-19.

The world has looked to the scientific community to rapidly discover treatment and preventative measures against novel coronavirus disease 2019 (COVID-19) in hopes of returning to normalcy. In turn, COVID-19 has become into a singular focus for the scientific community, with billions of dollars in research and development (R&D) funding continuing to be invested [1]. However, the collective response of scientific communities to the pandemic have seen poor return on investment, particularly for therapeutic research for COVID-19, revealing the existing weaknesses and inefficiencies of the clinical trial enterprise [1,2].

As of May 4th, 2021, there are over 2800 clinical trials registered for COVID-19 (covid-trials.org) [3]. The majority of these trials have not been designed to generate convincing and actionable evidence, and they have also been exclusive of low- and middle-income countries (LMICs), despite a large proportion daily COVID-19 cases and deaths occurring in these resource-limited regions [1,3]. Among therapeutic trials for COVID-19, there have only been 121 peer reviewed published articles that largely have not demonstrated convincing evidence for COVID-19 [4]. In contrast, there have also been a handful of clinical trials such as the RECOVERY, SOLIDARITY, REMAP-CAP, TOGETHER, ACTIV, and PRINCIPLE trials that have been designed to generate actionable evidence for COVID-19 [5–10]. These trials share a common characteristic of being a platform trial governed by a master protocol with international support and predictable long-term funding.

The "master protocol" terminology refers to a single overarching protocol designed to answer multiple research questions [11]. Master protocols aim to improve data collection and sharing with standardized operating procedures being implemented across multiple different institutions with centralized governance structure that create a large dynamic ecosystem for research. One type of master protocol is the platform trial, an extension of adaptive trial designs that allow for multiple interventions to be simultaneously compared against each other or against a common control with additional flexibilities of allowing new intervention arm(s) to be added and the standard-of-care to be updated during the trial [11].

Large platform trials are the ideal choice for clinical trial research aiming to determine the most effective therapy for an indication, and for COVID-19, where the science is changing every hour, platform trials may be the only choice. As there are usually large number of research questions that need to be answered quickly with standard-of-care evolving over time, clinical trials need to be nimble and dynamic in order to adapt to new internal and external scientific discoveries including changes in standard of care. There are, of course, challenges to conducting platform trials. Given their large scale and perpetual nature, setting up the master protocol of a platform trial can often be challenging and time-consuming [12–14]. While platform trials can offer statistical efficiencies by using a common control group and interim analyses, they may come at the cost of statistical complexities [15]. As the number of interventions and timing in which they are added to the platform can be hard to predict, standard procedures of adjustment for controlling for multiplicity may not be easily done despite there being multiple statistical comparisons being made [15]. For intervention arms that become added to the platform a significant time after the trial initially starts, there will already be data from patients who were enrolled and randomized earlier, in contrast to conventional randomized clinical trials where enrollment for all arms including the control arm will start at the same time. To account for the fact that new intervention arms may not be fully contemporaneous to the control arm, or

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vice versa if a new control arm is added, statistical adjustments must be made to avoid bias when making statistical comparisons with past control or intervention data [15]. To avoid potential issues with temporal variability, it is possible to limit the statistical comparisons of intervention arms with concurrent control in platform trials. In addition to the statistical complexities, there are operational complexities associated with running platform trials require careful consideration and usually a strong team of clinical trial experts [16–18].

Before the COVID-19 pandemic, master protocols and platform trials have largely been limited to the field of oncology and high-income countries, such as the United States (US) and the United Kingdom (UK) [19]. The COVID-19 pandemic has accelerated acceptance of master protocols and platform trials and also shown that principles of master protocols and platform trials can be tailored and adapted to research questions outside of oncology.

However, the accelerated acceptance of master protocols by the scientific community will not be enough. We need to recognize that current funding models act as a major hinderance to master protocols from being expanded to wider disease scope and geographical representation. There needs to be a shift towards new funding models where long-term investments towards a stable research infrastructure can be made for master protocols. In public funding models, a single agent or per-project based grant funding awards are most often awarded. As a result, public funding is mostly structured to test a single intervention-focused research questions one at a time to determine whether a given intervention can offer benefit over current standard-of-care or placebo. Even though different research questions may vary considerably in scope, the funding amount is also usually fixed for most grant applications. This can often result in an abundant number of short-term, underpowered trials that end up being conducted, instead of the finite funds being consolidated into a few larger master protocols. Under the academic reward structure that rewards individual contributions and publications with academic tenure, published trials even the underpowered and inconclusive ones can still be cited as individual contribution. Industry R&D programs usually have much larger funding, but similar to publicly funded trials, these programs still ask intervention-focused question only since the biopharmaceutical and medical device industries are focused on their individual asset. These companies are under significant pressure to quickly produce results that meet regulatory standards, so setting up individual trials may be viewed as the most rationale approach, since designing and obtaining regulatory and ethics clearance of master protocols can be time-consuming in the beginning. Further, pharmaceutical companies may be reticent to engage in data sharing and analytical strategies not developed in-house, creating barriers to engagement in existing master protocols. The current funding mechanisms only allow for short-term gains of individual academics or companies, and can neglect the patient needs.

Additionally, the current funding constraints for master protocols pose negative repercussion for global health [20]. Exclusion of LMICs in the clinical trial enterprise for COVID-19 may be partially explained by limited research infrastructure and local capacity. While these limitations can pose a challenge in carrying out clinical research, it is important to note that most regions have not been given a long-term opportunity to build and sustain an infrastructure that can be leveraged into improving local capacity with long-term training and professional development. With short-term funds, trial infrastructure usually disappears after the trial is completed, so keeping trained personnel at local sites is difficult.

Instead of funding a trial, we need a shift in thinking that funds a global evidence-generation infrastructure. Dedicated source of funding, whether philanthropic, government, or private, for long-term future of clinical trial research will be needed. We need to create a stable infrastructure by employing constant clinical research personnel and administrative support to the trial sites. For LMICs, this would mean there should be more equitable allocation of funds with local researchers and institutions. Long-term investments towards database design and management will need to be made, such that the database systems that can easily and accurately capture clinical trial data are created and maintained. Simplifying procedures and analysis in master protocols while keeping true its core principles, as the RECOVERY trial has done, will be important for future clinical trial research.

While it is difficult to imagine the world without COVID-19 right now, the time will (hopefully) come shortly. Valuable lessons gained from mistakes we have made during COVID-19 should not go away once this global pandemic is resolved. The scientific community has already embraced master protocols, but we need to improve the future of clinical trial research by removing barriers for master protocols. Proof of concept of phase for master protocols has firmly been established [11]. The next step is to institutionalize master protocols by setting up additional perpetual trials with extended disease scope and geographical representation from the current landscape of master protocols [19]. Regardless of their geographical origin, if academic investigators and private companies are offered the chance to participate after we build the long-lasting infrastructure for master protocols, we truly believe they will come.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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