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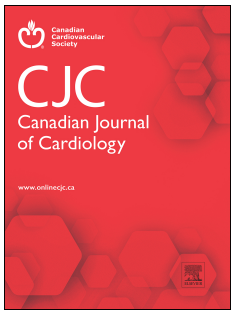

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The Impact of COVID-19 Research on the Development of Scalable Frameworks for Efficient Clinical Trials in Cardiovascular Medicine

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The COVID-19 pandemic has spurred the demand for prompt evaluation of possible treatments. However, conventional clinical trials' timelines for evidence generation proved inadequate. One of the most effective solutions has been the deployment of platform trials, which enable the simultaneous investigation of multiple therapeutic strategies. Platform trials operate under a comprehensive master protocol, that standardizes critical design and operational aspects, and incorporate adaptive elements, which enable modifications to the trial in response to its own data. Although platform trials and adaptive designs have been implemented in other fields, such as oncology, opportunity remains for their broader adoption in cardiovascular medicine.

The COVID-19 pandemic imposed an enormous burden on the healthcare sector. At the outset, no therapies were known to be effective against this new disease, and supportive care was the main pillar in the management of patients. Based on clinical anecdotes or biological reasoning, a number of existing drugs were proposed as candidates to be repurposed; new COVID-19 specific therapies were in the early days of pre-clinical development. Randomized clinical trials were urgently needed to evaluate the efficacy of these therapies. To achieve this, rapid mobilization of clinical trial networks was imperative. Clinical trials often take years to initiate – from hypothesis, to design, pilot phases, funding, definitive trial launch, and large-scale ramp-up of recruitment followed by trial closeout, and reporting. Such usual timelines would have been prohibitively slow. Newer models were needed to expedite trial execution during a rapidly evolving pandemic.

Epitomizing the difficulty of launching large-scale randomized trials in a short timeframe, initially a number of smaller trials sprouted in parallel. According to an assessment conducted by the Center for Drug Evaluation and Research at the US Food and Drug Administration, at the end of 2020, there were 2,024 COVID-19 trials registered worldwide, testing 2,895 different treatment regimens.[1] Only approximately 5% of these studies, however, were considered adequately randomized and powered.[1] Apart from power and ethical issues, multiple small trials investigating similar therapies may increase

the risk of type I error (false-positive result). These trials in many cases also competed with one and another for enrollment – potentially slowing evidence generation. In contrast, centralized approaches for coordinating collaboration and prioritizing investigational therapies, as shown to occur in the United Kingdom and the United States National Institutes of Health (NIH) Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) program, brought together investigators, funders, regulators, and site networks with remarkable efficiency for the purpose of conducting clinical trials in these jurisdictions. The trials that followed generated some of the most impactful evidence during the pandemic.

One effective solution employed strategies to implement novel platform trials. Platform trials are designed to study several therapeutic strategies for the same disease simultaneously, with therapy-specific arms being allowed to enter or leave the platform based on centralized decisions by the trial leadership as scientific knowledge evolves. Platform clinical trials improve clinical trial efficiency.[2, 3] Alternatively, other more traditional trial designs, such as factorial or multi-arm, could also be used to study multiple interventions. However, particularly during a pandemic, platform designs become more flexible by formally incorporating the addition or removal of intervention arms after the trial initiation.[4] For example, in the Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP; NCT02735707), at the time of writing, a total of 12,034 patients had undergone 21,242 randomizations, overall evaluating 61 treatments at 326 sites in a single platform trial (www.remapcap.org). The ability of such a trial to quickly generate new evidence cannot be overstated.

Platform trials operate under an overarching master protocol that contains standardized operating procedures and possibly standard definitions for eligibility criteria and outcomes. Instead of creating a new protocol for every new therapy, amendments to the master protocol are implemented to facilitate the evaluation.[4] A modular platform for data collection is harmonized and expanded or contracted as needed for each specific intervention. The control group often may be shared across

multiple interventions or be specific to a particular intervention arm to match evolving changes in standards of care or to comply with the specificities unique to that intervention (e.g., different eligibility criteria or need for a different placebo). Besides harmonizing clinical and data coordination centrally, platform trials allow the same study sites to potentially randomize patients to multiple treatments.[4] Operationally, such scalability is of immense advantage to facilitate the rapid initiation and efficient completion of clinical trials.

Platform trials frequently employ adaptive trial designs, allowing key design features to be modified in response to the ongoing trial's own data.[2] This approach can improve statistical efficiency and may facilitate earlier identification of effective therapies. For example, response-adaptive randomization allows randomization ratios to be modified, allocating more patients to treatments with increasing evidence of efficacy based on the blinded results of the interim analyses.[2] Such adaptation would decrease the number of participants randomized to an apparently less effective therapy, allowing the trial to prioritize treatment evaluation based on accumulating trial knowledge – speeding evidence generation for subjects within and outside of the trial. Group sequential stopping designs may also permit flexible sample sizes and optimize efficiency in trial design. A Bayesian statistical framework aligns well with adaptive platform trial designs, but is not required.[2]

During the pandemic, adaptive platform clinical trials have been used to generate clinical evidence rapidly. The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is an adaptive platform trial from the United Kingdom evaluating multiple interventions, such as dexamethasone, tocilizumab, hydroxychloroquine, and aspirin. As a pragmatic trial, RECOVERY focuses on the critical components necessary to produce high-quality evidence, facilitating quick trial implementation in a large number of centers – as of November, 2022, nearly 50,000 patients had been enrolled from 200 centers (www.recoverytrial.net). Linkage to national healthcare databases facilitated endpoint identification, reducing data collection by local teams. As a result, it took approximately three months

from the initial protocol draft for the enrollment of more than 10,000 patients. By June, 2020, only a few months into the COVID-19 pandemic, RECOVERY reported neutral findings for hydroxychloroquine and promising results for dexamethasone in hospitalized patients. Conducting similar initiatives in low- or middle-income countries is also possible, as exemplified by the Coalition COVID-19 Brazil. In the first months of the pandemic, a large clinical trial network was formed including more than 70 large centers across the country. Through a series of independent trials, the Brazilian investigators provided evidence concerning the use of hydroxychloroquine (alone or in combination with azithromycin), dexamethasone, and different anticoagulation strategies across a broad spectrum of COVID-19 severity, from the outpatient to the critically ill setting.

International collaboration has also been crucial for knowledge generation during the pandemic. The Solidarity trial, led by the World Health Organization, spanned across 600 hospitals from 52 countries, focusing on repurposed treatments for COVID-19. As discussed above, REMAP-CAP is a platform trial initially aimed at studying multiple interventions in critically ill patients with community-acquired pneumonia. This trial was started in 2014 and planned to pivot since its inception should a respiratory disease pandemic occur. When COVID-19 hit, a pandemic appendix was added to the core protocol, including some modifications in the eligibility criteria, primary endpoints, and statistical analysis plan. The previously assembled trial infrastructure could swiftly adapt to study multiple antiviral (hydroxychloroquine, lopinavir/ritonavir, inhibitors of the renin-angiotensin system), immune modulation (hydrocortisone, tocilizumab, sarilumab, anakinra, immunoglobulin), and anti-thrombotic (heparin and aspirin) strategies. By allowing a multifactorial design, the same patient could be randomized to multiple interventions, with a minority of patients receiving no active therapy.

Specifically for the study of anticoagulants, REMAP-CAP partnered with two other trial networks, the Canadian-led Antithrombotic Therapy to Ameliorate Complications of Covid-19 (ATTACC) and the NIH-sponsored ACTIV-4a trial.[5] Investigators from the three networks harmonized the

respective trial protocols into a single multiplatform trial, recruiting both critically ill and noncritically ill patients hospitalized for COVID-19. Similar eligibility criteria, interventions, data collection procedures, and outcome measures were adopted by the three platforms, and data were federated prospectively. Trial execution was expedited by the use of a flexible Bayesian adaptive design and frequent interim analyses. The REMAP-CAP/ATTACC/ACTIV-4a multiplatform trial involved almost 400 sites in 10 countries, and randomized the first patient in April, 2020. The trial studying anticoagulation strategies in critically ill patients was stopped in December 2020 when it met the a priori defined trigger for futility. In January, 2021 the trial focused on anticoagulation strategies for noncritically ill patients met the a priori defined criteria for superiority of therapeutic anticoagulation. As a result of the multiple collaborations, the multiplatform trial recruited approximately 3,500 patients in nine months, resulting in a scientifically robust and timely answer to inform anticoagulation use in patients hospitalized for COVID-19.[5] In the aftermath of the pandemic, REMAP-CAP continues to introduce new therapeutic domains to be tested in patients hospitalized with non-COVID-19 pneumonia, such as modulators of the endothelial function or alternative strategies for mechanical ventilation. Other platforms are also emerging, as is the case of the Platform of Randomized Adaptive Clinical Trials in Critical Illness (PRACTICAL), aiming to study therapies for patients with acute hypoxemic respiratory failure (https://practicalplatform.org/).

In conclusion, the COVID-19 pandemic highlighted that adaptive platform clinical trial designs, coupled with enhanced collaboration via federated networks-of-networks among investigators and trial sites, can dramatically improve efficiency to generate practice-changing knowledge. Platform trials and adaptive designs have a demonstrated track record in other fields such as oncology (e.g., the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy [STAMPEDE] trial and the Investigation of Serial Studies to Predict Your Therapeutic Response through Imaging and Molecular Analysis 2 [I-SPY 2] trial), but remain underutilized in cardiology. There is not, however, a reason why that should be the case. Although not a cardiovascular trial per se, the Strategies to Promote ResiliencY

(SPRY) is an example of adaptive platform trial investigating the effect of multiple perioperative interventions on hospitalization and mortality among elderly patients (NCT03861767). The first intervention being tested is metformin, and the core protocol allows for the addition of other therapies to be evaluated in the future. As shown by the previous examples, it may be time for cardiovascular investigators to build on the lessons and experience generated during the COVID-19 pandemic, developing a global framework for scalable collaboration, and potentially optimizing efficiency in cardiovascular clinical trials.

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