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EDITOR'S PAGE

Will COVID-19 Transform Translational Medicine?

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Non tutti i mali vengono per nuocere.
(Not all bad things come to hurt.)

The coronavirus disease-2019 (COVID-19) pandemic has caused massive global disruptions in clinical trial research, which will undoubtedly have long-lasting ramifications on medical science. At the same time, the health care exigencies created by the pandemic have forced regulatory agencies and investigators to reorient their approach to the way in which clinical research is conducted. Breakthroughs that once required decades to achieve are now occurring within months. As will be discussed, one positive outcome of the COVID-19 pandemic is that it may transform the way in which clinical trial research is conducted.

There are 3 areas where I believe that the pandemic may have a positive impact on cardiovascular translational research. The first is the manner in which clinical trials are designed and conducted. Although randomized, controlled, phase 3 clinical trials have been the gold standard for testing and validating new drugs and devices in cardiovascular medicine, they consume an enormous amount of time and effort. The complexity of cardiovascular clinical trials has resulted in these trials being increasingly more expensive. As discussed by Hwang et al. (1) in this Journal, the challenges of conducting cardiovascular research have resulted in a decrease in new cardiovascular trials entering clinical research. Germane to this discussion, the necessity to come up with effective new therapies during the COVID-19 pandemic has led to the widescale use of innovative adaptive clinical trial designs, including the multiarm, multistage (MAMS) platform trial design, which allows patients to be randomized to a control group or be enrolled in 1 of several different parallel arms that are being evaluated concurrently. Because MAMS platform trials use a common primary endpoint and use a shared control group, they are cost effective and efficient to run. Moreover, because MAMS trials are adaptive, they can drop ineffective treatments early for lack of safety or efficacy or add new therapies that appear promising. Two salient examples of platform trials that have been used during the pandemic are the Solidarity clinical trials sponsored by the World Health Organization (2) and the RECOVERY (Randomised Evaluation of COVID-19 Therapy) clinical trials sponsored by the United Kingdom (3). The Solidarity trial recently published interim results in 12,000 patients and reported that all 4 of their lead candidates, including remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon had little or no effect on overall mortality, initiation of ventilation, and duration of hospital stay in hospitalized patients (2). The RECOVERY trial also reported that hydroxychloroquine was ineffective in hospitalized patients; however, RECOVERY did show that treatment with dexamethasone resulted in a lower 28-day mortality among patients who were receiving either invasive mechanical ventilation or oxygen alone but not among those receiving no respiratory support (3). Two other innovative adaptive trial designs deserve further mention. The AGILE (Accelerating COVID-19 Drug Development) trial is an example of a randomized, seamless, phase 1/2 trial in which multiple different candidate treatments undergo dose escalation to establish the safety profile of candidate drugs in different patient populations (4). Safe compounds can then be advanced, and the efficacy of the compound can be assessed via a randomized Bayesian group sequential trial. The AGILE trial design allows for parallel efficacy evaluations of different compounds and is seamless insofar as the efficacy data

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obtained during the dose escalation phase of the trial can be used in the efficacy phase as well, and the safety information from the efficacy phase can contribute to the safety database for the dose escalation phase. After evaluating the efficacy data, a treatment can be dropped for futility or progressed to a definitive trial. Another innovative trial design is REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia), which was designed to evaluate multiple interventions to improve outcomes of patients in the intensive care unit with severe community-acquired pneumonia. REMAP-CAP also had a prespecified data analysis plan to evaluate respiratory pandemics (4). In REMAP-CAP, patients are stratified by disease state (e.g., hospitalized or ICU) and then receive 1 intervention from several mutually exclusive domains (e.g., antiviral, immunomodulatory). The trial is adaptive so that new interventions (e.g., a new antiviral) or new domains (e.g., steroids) can be added or dropped. Patients are randomized to a regimen that consists of 1 intervention from each of the domains, using response-adaptive randomization to adjust the ratio of patients who are assigned to each treatment regimen so that more patients are allocated to the most promising treatment algorithms (4). Although these types of innovative adaptive approaches have not yet been used in cardiovascular clinical trials, they could be.

The COVID-19 pandemic has had devastating effects on how clinical trials are conducted. One of the major disruptions during the pandemic has been the requirement for physical distancing to protect patient and researcher safety. This obstacle gave rise to the increased use of decentralized clinical trials, which are trials executed through telemedicine and mobile/local health care providers (5). In addition to decreasing the cost of performing clinical trials and allowing for more rapid implementation of clinical trials, decentralized clinical trials may also increase trial access for women, individuals of minority groups, and vulnerable patient populations. Although decentralized clinical trials are not appropriate for all therapies, the decreased cost and relative ease of implementation may have lasting implications for how clinical cardiovascular trials are conducted in the future. The third area where COVID-19 may affect translational clinical trials is how it may change the role of Data Safety Monitoring Boards (DSMBs) in the future. As discussed in this column in June 2020 (6), the issues surrounding the recommendation of the DSMB to stop the ACCT-1 (Adaptive COVID-19 Treatment Trial) after it met the primary endpoint (shorter time to recovery from COVID-19), rather than continuing the trial to ascertain whether there was a potential mortality benefit, raised important questions about what the role of DSMBs should be in the future. DSMBs are in a unique position insofar as they are able to review unblinded clinical trial data while they are accumulating and provide recommendations to the sponsors with respect to whether a trial should continue as planned, be modified, or be terminated. Although DSMBs frequently make recommendations to terminate trials early for harm, futility, or benefit, they are not empowered to make recommendations to extend clinical trials for non-pre-specified endpoints. As we noted previously, the "ACCT-1 trial controversy illustrates the tension between the competing goals of clinical research: the production of ideal scientific knowledge that benefits society—in this case mortality outcome data—with the protection of individual participants in the face of a deadly pandemic; and the need to make treatments quickly available to very sick patients. . . Nevertheless, broadly recognized principles of public health ethics require that we infringe as little as possible against competing values or priorities such as knowledge regarding survival in clinical trials as we pursue a goal such as providing acutely ill patients with a proven intervention" (6). Given that DSMBs are uniquely positioned to make informed decisions about what may be in the best interest of public health based on the unblinded data that are available to them as a clinical trial is being conducted, the question arises as to whether they should also be empowered to act on this knowledge.

I chose to begin this "Editor's Page" with an Italian proverb—"Non tutti i mali vengono per nuocere (not all bad things come to hurt)," not because I am blind or numb to the human pain and suffering caused by the pandemic, but rather because the English version of this proverb is "Every cloud has a silver lining." If there is a silver lining to the COVID-19 pandemic, I suspect that people will perceive the silver lining differently depending on their own personal circumstances. As a cardiovascular translational scientist, one potential silver lining of the COVID-19 pandemic that I can envision is that the virus has forced us to rethink and reimagine the way in which we develop and test new therapies, which may, in turn, change the way that we develop new cardiovascular therapies. As always, I welcome comments and suggestions from investigators in academia and industry,

patients, societies, and all of the governmental regulatory agencies regarding your thoughts about how the COVID-19 epidemic will positively or negatively affect cardiovascular translational research, either through social media (#JACC:BTS) or by e-mail (jaccbts@acc.org).

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