EDITORIAL

Randomized Clinical Trials and COVID-19
Managing Expectations

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Despite the millions of cases and hundreds of thousands of deaths that have occurred in this devastating coronavirus disease 2019 (COVID-19) pandemic, no peer-reviewed studies of specific therapies proven to be effective in reducing mortality have been published and a vaccine is many months to years away. To date, more than 1000 studies addressing various aspects of COVID-19 are registered on ClinicalTrials.gov, including more than 600 interventional studies and randomized clinical trials (RCTs).[1] During the next few weeks and months, the results of numerous RCTs involving therapies for COVID-19 will be reported. Indeed, preliminary results from some studies have already been reported in social media and the popular press. How will clinicians, the public, and politicians understand the results of these much-anticipated and critically needed clinical trials?

First, the interventions in some of these trials are being evaluated in various ways. For instance, some studies do not have a control group, whereas others lack true "controls" such as trials that compare different dosages of the same drugs. This will limit the inferences that can be drawn, likely necessitating further research to define the true benefit of a specific treatment. In addition, in some trials, the investigational agents are administered in combination with multiple other therapies given at various time points in the disease process. Without rigorous design and attention to trial protocols for study drug administration, there will be challenges disentangling the true effect of the intervention.

Second, many ongoing trials were designed prior to emerging information that is providing a better understanding of the disease process. It has become clear that some critically ill patients with COVID-19 have substantially different manifestations, including profound hypoxia, extensive inflammatory activation, or evidence of coagulopathy. Accordingly, there may be significant heterogeneity of treatment effects based on the timing or constellation of disease manifestations. It is possible that an antiviral agent or other agents, such as those directed against inflammatory markers (ie, certain cytokines), could be helpful for critically ill patients who do not have overwhelming inflammation but would not be effective for patients in whom the inflammatory cascade is markedly activated. Given that the size of many ongoing trials is limited, few investigations will be appropriately powered to conduct meaningful secondary and subgroup analyses. Most additional analyses should likely be considered exploratory.

Third, the outcomes for many of these trials involve time to symptom resolution, improvement of laboratory or radiographic abnormalities, or reduction in the use of mechanical ventilation. Few of the studies will be sufficiently powered to detect a difference in mortality. Although these are important clinical outcomes, and use of mechanical ventilation is associated with mortality, it will be important to objectively assess and accurately describe the outcomes from ongoing trials and what the results potentially mean in terms of improving overall survival. In addition, for trials with unblinded treatment allocation and unblinded outcome assessment, interpretation of findings, such as symptom resolution, may be problematic.

Fourth, even a highly successful trial is likely to reduce the mortality outcome by only a 5% to 10% absolute difference; hence, the number needed to treat will be a minimum of 10 to 20. Smaller absolute differences would have greater numbers needed to treat. This remains a challenging issue for clinicians and patients to understand. Given these likely numbers needed to treat, most patients will not benefit from even a successful treatment. Moreover, even though there have been reports of studies that some interventions have reduced the duration of intubation or length of hospital stay represent progress against COVID-19, these findings do not indicate that patients with this disease are "cured" with the drugs used in these investigations.

Fifth, most of these trials are directed at treatment, and even if some trials show clinically important results, most will not address prevention of COVID-19. The results of these trials (most of which are being conducted among hospitalized patients in whom the disease is well-established) might not necessarily be directly applicable for altering the incidence of disease in the coming months or preventing future surges of disease. Numerous observational studies using existing databases are being conducted to determine whether the use of certain drugs is associated with COVID-19 disease outcomes, such as whether hydroxychloroquine is associated with less disease, or whether use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers is associated with an increased risk of disease. However, these will be observational studies with all the attendant limitations. Accordingly, the findings of rigorous clinical trials of vaccines and possible other therapies will be essential in determining how to effectively prevent COVID-19.

Sixth, it will be helpful if investigators share individual patient data from similar trials with one another. This will allow for additional analyses, even if the analyses of the combined data were not preplanned and would be considered exploratory. The goal is to expand what is known about possible treatments, so that future trials can be improved, perhaps by using approaches such as large adaptive platform trials.

The clinical trials community around the world, in conjunction with numerous funders, has rapidly mounted important RCTs during the COVID-19 pandemic. This is a remarkable achievement. However, presenting and interpreting the results of these studies clearly, and communicating findings appropriately to clinicians, the public, and policy makers, is critically important. Because much of the focus is now on preventing recurrence of the pandemic, it will be important for investigators, journals, and the media to accurately report the results of the studies responsibly and what they mean both for individuals and for population health.

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