Letters

Editor's Note

Setting Expectations for Clinical Research During the COVID-19 Pandemic

"Knowing and understanding an epidemic is the first step to defeating it." Since Tedros Ghebreyesus, PhD, Director-General of the World Health Organization, tweeted this on March 2, 2020,[1] coronavirus disease 2019 (COVID-19) has become a pandemic that has claimed hundreds of thousands of lives. The medical and research community has mobilized with unprecedented rapidity to address knowledge gaps for this novel disease.

In this issue of *JAMA Internal Medicine,* Pundi et al[2] provide an early barometer for the clinical research response to COVID-19. Using ClinicalTrials.gov, they found 1551 studies registered on COVID-19 as of May 19, 2020. Although this work is impressive in quantity, the authors concluded that fewer than one-third of these studies were designed to provide evidence strong enough to be potentially practice changing. Mortality, arguably the most important outcome, was rarely a component of the primary outcome for randomized clinical trials.

These data are an important reminder that we should manage our expectations of initial studies.[3] Small cohort studies in the initial phase of a new pandemic serve to delineate the patient population in the context of current treatments for the planning of future research. However, multiple, small, flawed trials will not give us the answers we need to treat this disease. Although the product of lower research standards may be marginally more useful than knowing nothing, we must seriously consider the potential harms of disseminating invalid findings mined from convenience samples or poorly controlled or underpowered studies. Equally important to managing expectations is for the clinical research community to set expectations. We should not sacrifice well-designed trials in the haste to generate new knowledge. Given the high stakes, all of us—clinicians, researchers, research funders, research regulators, and research publishers—are responsible for ensuring that the scientific value derived from conducting the trial justifies the risk our patients bear when they participate and their expectations of contributing to societal good.

In diseases such as COVID-19 that have a rapidly changing disease landscape and evolving standards of care, adaptive trial designs[4] can allow research to respond nimbly but still maintain a valid control arm by using interim results and new standards of care to launch new study arms while allowing early stopping for efficacy, safety, or futility. The World Health Organization recommends using a consistent primary outcome between COVID-19 therapeutic trials and proposes an ordinal scale for clinical improvement to be responsive to the patient population and disease course. This is similar to a traditional composite end point, except it ranks component events, with mortality ranked as the most clinically important outcome.[5]

There are many ways to promote collaboration and efficiency. Can our patients coenroll in multiple studies? Can we use the same control group for multiple trials? How do we fast-track rate-limiting steps in research such that clinically overloaded or research-naive sites can easily participate? As we adjust to post-COVID-19 life, it is important that we take steps forward, not backward, in research.

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