Rethinking Clinical Trials Reform During the COVID-19 Pandemic

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Most of the 1.8 million US patients each year who are diagnosed as having cancer remain alive 5 years after diagnosis. This success can largely be attributed to clinical trials that have studied novel anticancer therapies in addition to advances in surgical techniques, radiotherapy, and supportive care. We have achieved this progress despite the fact that fewer than 10% of adult patients with cancer in the United States enroll in clinical trials. One can only imagine the magnitude of benefit that patients would experience if we improve and accelerate clinical trial enrollment. Many scholars have outlined barriers to participation in clinical trials and proposed strategies to overcome them, but despite these ideas, little progress has been made. A new, unforeseen barrier has been the emergence of severe acute respiratory syndrome coronavirus 2 causing the coronavirus disease 2019 (COVID-19) pandemic across the globe. While this pandemic has impeded and slowed clinical trial enrollments, we view this unfortunate event as an opportunity to reform the way we conduct clinical trials moving forward. Herein, we examine several changes precipitated by the current crisis that represent potential areas of improvement for the future.

First, clinical trials are often only available at academic medical centers and frequently require face-to-face visits. Commonly, these visits occur much more frequently than what standard practice follows. As such, the logistical aspects of enrollment represent major barriers to participation. These in-person visits can make it difficult for patients, increasing out-of-pocket expenses and requiring them to be absent from work, while also being particularly prohibitive for patients traveling from afar. However, the COVID-19 pandemic has led to the widespread adoption of telemedicine and virtual visits. The Centers for Medicare & Medicaid Services and private insurers across the board have embraced these virtual platforms as they are currently safer for patients, minimizing the risk of unnecessary exposure for patients and clinicians. We foresee clinical trials becoming more flexible and embracing this “new normal,” limiting in-person visits only to those that are necessary. This, of course, requires finding avenues for enrolled patients to have access to a secure virtual platform. Extending virtual support for patients would hopefully lead to an increase in participation in clinical trials.

Second, many clinical trials do not allow laboratory studies or procedures to be performed outside of the center where the trial is being conducted, even if patients live far away and have the resources to do laboratory studies or procedures locally. In fact, the stringent requirements and the frequency of these tests and other study-related procedures (ie, frequent electrocardiograms for phase I studies) have been a major barrier for patients’ enrollment in clinical trials. The COVID-19 pandemic has led some sponsors and regulatory bodies to be more flexible and agree to have tests done locally and less frequently. Why is this not the normal process? Because basic laboratory tests are standardized (eg, complete blood count, chemistry) and the pathology of a tissue biopsy or a bone marrow needs to be reviewed centrally, we see no reason why these routine and basic tests cannot be performed at the location most convenient to patients, provided no special expertise is needed.

Third, this pandemic has led some contract research organizations (CROs) to become more reasonable in their inquiries and requests, which require daunting administrative tasks of busy researchers and their staff. Many in the oncology community feel strongly that these requests are not necessarily made based on patient safety or study-related integrity. These requests, which can be overwhelming, are often at odds with the goals of investigators, sponsors, and ultimately the patient community, as the burden of administrative work surely limits study enrollment and a center’s capacity to open additional studies. At the request of regulatory bodies, patients, and sponsors during the current crisis, some CROs have adjusted study oversight in very noticeable ways. Owing to many research site restrictions, CROs have been forced to be on site less frequently, and therefore have increased Health Insurance Portability and Accountability Act-compliant remote monitoring practices to maintain their role of ensuring the quality of collected data. As such, the pandemic has been a proof of concept, demonstrating that institutions need to carefully examine the frequency of in-person monitoring requests in the future and consider requiring off-site monitoring more often to improve efficiency. We argue that these new practices need to be maintained in the aftermath of the COVID-19 pandemic to facilitate advances in oncology. We are thankful as a community for the US Food and Drug Administration to have rapidly issued general considerations to assist sponsors in ensuring the safety of trial participants while maintaining compliance with good clinical practice and minimizing risks to trial integrity during this public health emergency. In addition, in cases where sites may not be able to meet all requirements of a trial protocol, some organizations have relaxed their outlook of timely data entry and protocol deviations. For example, NRG, an international cancer clinical trials network group funded by the National Cancer Institute encourages investigators to explore alternative methods for obtaining data, such as telehealth visits, but adds that member sites will not be penalized for data delinquencies or protocol noncompliance during this time period. Moreover, many clinical trials explor-
ing vaccines or anti–COVID-19 therapies started recruitment in record time, a process we hope can be applied to cancer trials, especially those targeting critically ill patients.6

Fourth, most clinical trials require frequent imaging studies to assess disease status. Some of this is driven by the fact that many trials use progression-free survival as the primary end point for efficacy, mandating frequent imaging to detect timely progression. In the COVID-19 era, imaging studies are being delayed even for cancer patients receiving antineoplastic therapies. Emerging guidelines from the US Food and Drug Administration suggests that tumor assessments, when appropriate, may be delayed for ongoing trials.4 This would never have been normal before this pandemic. Decreasing the frequency of imaging studies, when applicable, would be a welcome change for patients, sponsors, and payers; the opportunity to expose patients to less radiation and iodinated contrast and to reduce an incredible component of study-related costs should be welcome by all. Even 1 less imaging modality (eg, computed tomographic scan) during a 1-year time frame will lead to cost saving. However, we need to exercise caution because progression-free survival as an end point is heavily dependent on frequent tumor measurements. One way to mitigate this concern is to gradually increase time between imaging studies when designing the trials or to designate overall survival as the primary (or co-primary) end point in more studies. Obviously, each follow-up requirement is different depending on the particular tumor, but an effort can be made to at least match trials’ imaging requirements with general national guidelines.

Fifth, in the absence of frequent imaging studies, oncologists have to make decisions on whether to continue or discontinue a treatment regimen based on the patient perspective, redefining “clinical stability” in terms of how patients feel. This shift due to the pandemic underscores the importance of patient-reported outcomes, which have been shown to improve overall survival in cancer patients.7 In addition to efficacy, we propose that investigators continue to add patient-reported outcomes as another end point in future studies because these measures have inherent value to patients.

Sixth, we are still managing cancer in patients based on best clinical judgment and emerging clinical information about the pandemic. It is fair to say that whether the changes in the way we conduct clinical trials during the pandemic is optimal in terms of patient safety and measurement of outcomes have not yet been studied. Only with longer follow-up will this be determined. We argue that this pandemic offers great opportunity to explore these questions by conducting real-world evidence studies to pragmatically test whether these implemented changes during the pandemic were detrimental or helpful to patient care. These studies cannot answer which methods for conducting clinical research are more effective and efficient because only randomized clinical studies can answer these questions decisively. One example includes the COVID-19 and Cancer Consortium, which aims to collect and analyze observational data at scale (through crowdsourcing) to inform clinical practice in real time.8

It has taken a pandemic and a relentless virus for the medical community to start thinking critically about various aspects of patient care and clinical trials. Through the necessary reforms implemented for medicine to survive in the face of this crisis, we hope that we can find a silver lining in improving how we execute clinical trials going forward for the betterment of cancer patients.

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REFERENCES