Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Multicenter Clinical Cancer Research After COVID-19: A Perspective From NRG Oncology

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The World Health Organization declared coronavirus disease 2019 (COVID-19) a pandemic on March 11, 2020. By March 26, the United States had the highest number of confirmed cases in the world. COVID-19 has had a profound impact on cancer care and cancer-related clinical trials. Its effects were perhaps most dramatic beginning in late March 2020 when many health care institutions either limited or shut down their elective services, including research, in preparation for the pandemic.

In this ongoing phase of the pandemic, many patients seek to limit the time spent at health care facilities and face difficult decisions about whether to enroll in a trial or, if already enrolled, to continue protocol therapy and follow-up. Physicians and research staff are being pulled in many directions, trying to balance on-site work, remote work, and unexpected personal challenges such as child care gaps, ill relatives, and/or financial issues. They may not have the time or energy to discuss clinical trials with patients and proceed with the workload involved with study enrollment and trial conduct. Health care institutions are also suffering financial losses that can result in research being de-prioritized.

Not surprisingly, there was a significant decline in enrollment onto National Cancer Institute (NCI) National Clinical Trials Network (NCTN) group clinical trials in April and May of 2020. Figure 1 shows weekly accrual to the interventional studies of the NCTN and NRG Oncology, 1 of the 5 multicenter groups that make up the NCTN. A dramatic decline in enrollment began in March 2020, reaching its nadir in April. Although there has been an enrollment recovery in May and June 2020, as of writing this article, accrual has not returned to pre-pandemic levels. This pattern is similar to that seen in other international groups.[1,2]

In addition to decreased enrollment, which will delay trial completion, there have been challenges with maintaining trial procedures and data quality. Some patients have canceled scheduled visits, scans, and laboratory draws; facilities have reduced available services; and research coordinators may have reduced work schedules or decreased access to physical study binders, causing delays in data entry. External auditors, including those from the NCTN groups, are often limiting site visits to review paper study binders.

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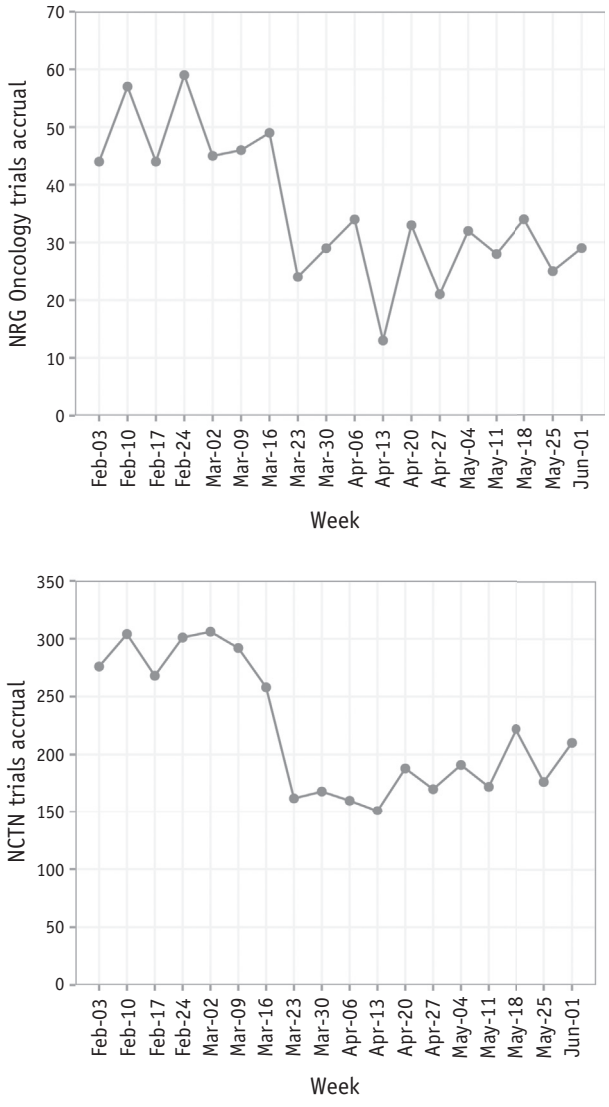

Fig. 1. Weekly accrual to NRG Oncology and National Clinical Trials Network interventional studies from February to June 2020.

The NCI and NCTN have recognized the difficulties faced by patients and investigators and have made accommodations to improve the feasibility of conducting clinical research during the pandemic and the subsequent recovery.[3] For instance, the research team can ask a local health care provider to temporarily administer standard-of-care study treatments if the patient is unable to travel to the study site. Patients can provide consent remotely, although the process can be cumbersome. As an example, if postal mail is to be used, the team would mail 2 copies of the consent form to the patient, check with the patient to see if the forms have arrived, review the form with the patient over the phone, ask the patient to sign 1 copy and mail it back, wait for receipt of the signed consent form from the patient, attest with their own signature(s), and then mail a copy of the final signed form back to the patient. In a time of reduced staffing and remote work, such complicated workflows could hamper or delay enrollment.

It is possible that the pressures of this crisis will spur innovation and will result in lasting improvements in the clinical trials enterprise. Three priorities are listed that existed before COVID-19 but are now even more crucial to achieving progress in cancer research.

First, the use of telehealth and digital medicine technologies can make clinical trials accessible to a broader group of patients. For routine clinical care, there has been an explosion of the use of telehealth such as video visits. Many providers and patients have been surprised and pleased by how effective telehealth can be. Patients who started using video visits during the peak of COVID-19 may become accustomed to them and continue to receive much of their health care remotely. If this evolution in care can be incorporated into clinical trials, it will allow research participation to be more feasible for those who live in rural areas or have mobility or financial challenges that preclude frequent in-person visits. It is well known that there are disparities in clinical trial participation according to race, ethnicity, age, and income.[4,5] It is possible these could be reduced via the use of telehealth. Vital sign collection, activity monitoring, and even neurocognitive testing could be done at home, harnessing technologies such as smartwatches and other wearable sensors. Of course, requiring access to a smartphone and high-bandwidth connection could be a barrier to participation for some patients, especially those with lower socioeconomic status.[6]

Second, the increase in remote work among research coordinators and network group staff compels a reassessment of the ways that trial data are recorded, stored, monitored, and audited. Many centers still use binders to hold paper consent forms, eligibility checklists, and printed laboratory values. They rely on research staff to manually enter data into trial databases. This system is inefficient, costly, and error-prone. Electronic health records can be connected to research database systems, so eligibility verification is easier, accuracy of data collection is increased, and patients can be screened more automatically for trials. Progress on interoperability has been painfully slow despite many words written and standards drafted. The efforts of the National Institutes of Health in this space are commendable,[7] and regulators are encouraged to consider steps such as requiring that electronic health records be able to communicate with the electronic data capture systems used for federally funded trials.

Finally, it is hoped that the constraints caused by the current pandemic will encourage efforts to streamline eligibility requirements for clinical trials.[8] This could help to increase enrollment rates and make trial participants more representative of the broader population. Eligibility criteria are often carried forward from older protocols and

may not logically apply to the interventions in the new protocol. Time windows for scans or laboratory results could be made less restrictive—currently, many patients may not be interested in repeating a scan to enroll in a trial. It can also be a challenge to match patients to trials that require a specific tumor mutation that may only be present in single-digit percentages of patients. The use of master protocols should be encouraged, including basket, umbrella, and platform trials, which can evaluate multiple therapies or multiple disease subtypes within the same trial.[9] Some examples include NCI-MATCH and NRG-GI002.

It will be fascinating to see how the network groups such as NRG Oncology and medical centers adapt to the changes that have occurred during the pandemic. Some have claimed that the traditional clinical trials enterprise will be disrupted in the way that photographic film manufacturers and video stores were in the past.[7] Large technology companies are investing billions in health care initiatives and ambitious digitally focused studies. The publicly funded NCTN system led by academic scientists, at its best, has a clarity of purpose that cannot be replaced by the work of for-profit companies. There is no substitute for carefully curated cancer outcomes data obtained from traditional prospective randomized trials. The community needs to think energetically and critically on how to streamline research workflows while maintaining the safety and privacy of the participants who place their trust in this work.

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