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The World of Clinical Trial Development Post COVID-19: Lessons Learned from a Global Pandemic

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ABSTRACT

The novel coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is a global health threat (1). Patients with cancer are one of the most vulnerable populations. During this pandemic, clinical trial accrual to NCI studies has fallen dramatically. Investigators quickly turned to regulatory bodies to simplify treatment schedules, facilitate telemedicine, and decrease required data collection. Going forward, the oncology research community must use the lessons learned to focus on redesigning studies to ensure that critical scientific questions are answered safely while expanding access and increasing partnerships with community physicians. These changes will accelerate clinical progress while protecting our patients.

Introduction

As COVID-19 has disrupted daily lives across the globe, it has also caused a decrease in clinical trial accrual for oncology patients. When our most vulnerable patients need treatment, and cannot access oncologic health care, what is the best way forward? Until now, oncology clinical trial design and implementation has not changed in a meaningful way in decades. However, in response to the pandemic, oncologists have adopted telemedicine, community partnerships, and simplified protocols to protect patients while maintaining the integrity of studies. Patients and investigators have quickly embraced many of these changes and it has become clear that embracing these changes is imperative.

Clinical Trial Eligibility Criteria

The first step in redesigning oncologic clinical trials includes modernization of eligibility criteria. Eligibility criteria define characteristics of the patient population that qualify for a clinical trial (2). Over time, some eligibility criteria have been accepted without scientific merit making trial participation restrictive. The NCI has championed broader eligibility including factors such as age, comorbid conditions, secondary malignancies, history of infectious diseases (hepatitis and HIV), and organ dysfunction as a part of the American Society of Clinical Oncology and Friends of Cancer Research Working Group (3). As of November 2018, new inclusion/exclusion criterial were required for NCTN and ETCTN clinical trials (4). We should follow these guidelines to extending trials to a broader population encouraging inclusiveness and promoting the generalizability of study findings (4). Historically, narrow eligibility criteria has been an issue throughout oncologic clinical trials (5), but now, more than ever, is a time to expand while protecting the safety of patients.

Correlative Studies

Correlative laboratory studies are common secondary objectives in clinical trials (6). Scientific review committees often require these studies, yet often little critical review is done on the feasibility or likely impact of the studies. Blood may be collected, or biopsies obtained at protocol mandated times that are unlikely to yield meaningful information but increase the complexity and risk for patients. Biomarker development is a challenging and complex process and while there have been successes in oncology such as targeting the overamplification of HER2, there exists a large gap between biomarker discovery and clinical translation (7). Correlative studies that incorporate biomarker development need critical thought in protocol design.

Serum and tissue from studies is vitally important in making progress in cancer research, yet often it is only after the trials are completed that one can properly determine the most important correlative studies. Thus, studies should certainty strongly encourage collection of serum and tissue but should only mandate laboratory studies that are well powered and potentially impactful. In preparing for a world during and post-COVID-19 infections, flexibility needs to be incorporated into protocols for obtaining correlative blood, tissue, and other samples through community physicians and laboratories with collaboration with private insurances and federal/state programs.

Telehealth

COVID-19 has forced the medical community to adapt quickly to telemedicine and telehealth. Health care systems have shifted from scheduled office visits to telemedicine visits to limit travel, infectious complications, and to promote continuity of care (8). The traditional clinical trial model limits clinical trial participants to one or a handful of sites in which to receive treatment. This model makes accrual more difficult and the COVID-19 pandemic has shown access to quality care is hindered in racial/ethnic minorities (9) and rural areas (10) of the United States. Decentralization of the model, in which patients can be evaluated via telemedicine can be incorporated, particularly for follow-up visits. Protocols need to be written to collect only the data that are scientifically important. A study may only want to only collect a physical exam of clinically relevant areas at each visit that could simplify telemedicine visits or data collection from community partners. Studies should also allow validated devices to track vital signs such as temperature, blood pressure, and heart rate. Close partnerships need to be maintained with community oncologists to ensure safety if adverse events are discovered during a virtual visit. Importantly,

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Translational Relevance

COVID-19 infections pose a serious risk for many patients with cancer. Physicians are making treatment decisions in an attempt to decrease the likelihood of immediate infectious harm with the hope of few long-term negative cancer consequences. At the NIH, Center for Cancer Research (CCR), clinicians have carefully evaluated each patient and after consulting with the Institutional Review Board and sponsor(s), have attempted to decrease required tests and patient visits to the Clinical Center while maintaining patient safety and the scientific integrity of clinical trials. Going forward, this will likely impact how the oncology community conducts clinical trials, as studies are designed to ensure that we collect only the information that is scientifically important and explore what aspects of a clinical trial can be performed outside tertiary cancer centers without diminishing the scientific impact of the study and the safety of our patients.

remote informed consent procedures should be implemented into trials for patients who cannot travel to study sites due to socioeconomic pressures or health risks. Telehealth can also incorporate digital transfer of relevant imaging scans and digital pathology (11). Advances in digital technology and artificial intelligence make telehealth exciting and meaningful for patient care on oncology trials.

To facilitate medication administration, clinical trials should have a process to mail oral medications to patients throughout the country. For IV study medications, agreements can be implemented between tertiary centers, the FDA, sponsors, and community physicians to treat patients locally. The use of a central Institutional Review Board (IRB) can help facilitate a centralized review process, increase efficiency, monitor safety, and address issues between sites (12).

Cost is an ever-present concern in oncology clinical trials and due to COVID-19 changes in reimbursement have already started to be implemented due to telehealth. The Centers for Centers for Medicare and Medicaid Services have modified payment policy in response to Covid-19 and telehealth visits (8). In the future, postpandemic, mechanisms for reimbursement to community oncologists, laboratories, imaging centers, and infusion centers will need to be structured into clinical trials.

Clinical Trial Partnerships

Allies in the goal of expanding and maintaining clinical trial participation includes patients but also community oncologists and primary care physicians. IRB and sponsors must work together at the time of trial design to permit, when possible, study treatment to patients close to their homes. This should be a true research partnership with fluid communication and potentially a member of the community oncologist's team on telehealth calls led by a tertiary care center. Community oncologists should have input into the study with a focus on the logistics of the trial. These partnerships could reach patients beyond those who seek out clinical trials, thereby increasing accrual rates and increase representation of minorities and women in clinically trials that historically been suboptimal (13).

Future Directions

Clinical trials in oncology have always been conducted with patient safety as the highest priority, but that must now take on an added dimension as the logistics of treatment administration and follow-up are redesigned to maximize patient well-being while minimizing travel. As "No man is an island, Entire of itself" (14), medical oncologists are a part of a vast community who will need to partner together to expand scientific discoveries. The first step is to critically evaluate how we are writing and implementing clinical trials and to be cognizant that the time is now to change and adapt as the world changes.

Conclusions

COVID-19 has taught the medical community flexibility is key for patient care, particularly in clinical trials in patients with cancer. The safety of our patients and staff are paramount. As such, these unique and trying times have given the oncology community an opportunity to improve clinical research by removing restrictive eligibility criteria, fostering partnerships with the broader medical oncology community, incorporating telemedicine and telehealth, reaching underserved populations, and storing research blood and tissue for future use.

Disclosure of Potential Conflicts of Interest

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Disclaimer

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