

Lessons From the Impact of the COVID-19 Pandemic at the National Cancer Institute

Cancer Research and Care

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Abstract: The COVID-19 (coronavirus disease 2019) pandemic has worldwide implications on health care, especially in our most vulnerable population: cancer patients. Flexibility and adaptation are needed to continue clinical research and for clinical trial development. At the Intramural Research Program, National Cancer Institute, swift changes have been implemented to protect our patients while maintaining the scientific integrity of our cancer clinical trials. Many lessons have been learned including incorporation of telehealth into clinical trials, partnerships with the oncology community at both academic institutions and community practices, focusing on diversity and inclusion to improve scientific innovation, and strengthened relationships with regulatory agencies and institutional review boards. These changes will enhance the clinical trials we conduct well beyond the pandemic.

Key Words: Clinical trials, correlative studies, COVID-19, diversity, inclusion, intramural research program, NCI, NIH, oncology, pandemic, remote consent, telehealth

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The National Institutes of Health (NIH) is the world's largest biomedical research agency and comprised 27 institutes and centers, with specific research agendas. The Cancer Act of 1937 established the National Cancer Institute (NCI) as the focal point for the nation's cancer research efforts. The NCI Center for Cancer Research (CCR) is the largest division of the NCI's intramural research program with nearly 250 basic and clinical research groups¹ and a myriad of research goals including cancer prevention, treatment, and HIV/AIDS research. Patients are treated in the NIH Clinical Center (CC), known as America's research hospital, with multiple unique facilities and programs to support clinical trial research. Every cancer patient at the CC is followed or treated on a research study, and patients travel from all 50 states, and internationally, to be evaluated. Importantly, neither patients nor health insurances are billed for medical care provided at the CC, and health care is delivered in partnership with the patient's local medical team. Unfortunately, the novel coronavirus disease 2019 (COVID-19) affected medical care across the globe, but particularly one of the most vulnerable populations—cancer patients—especially those cared for at the NCI. Because of the COVID-19

pandemic, clinical trial accrual at the NCI fell dramatically, and investigators quickly determined changes that were imperative to continue clinical research and serve our patients.

COVID-19, caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), was first recognized in December 2019² and has since disrupted oncologic care and particularly cancer clinical trial accrual across the globe.³ In March 2020, the American Society of Clinical Oncology launched a survey to assess clinical trial challenges early in the pandemic.⁴ Data analyzed from 32 survey respondents revealed a substantial impact on clinical trials on multiple levels including halting screening or enrollment on certain trials and halting research-only visits as well as research-only blood and/or tissue collections.⁴ The National Clinical Trials Network and the Experimental Therapeutics Clinical Trials Network analyzed accrual and demographics in both 2019 and 2020.⁵ Accrual fell in mid-March 2020 and began to recover in June/July 2020,⁵ but the COVID-19 pandemic impacted many aspects of clinical trial conduct including the temporary halting of new trials (particularly phase I studies), complex trials, and specimen processing. A cohort study evaluating the 1-year experience of cancer clinical trial enrollment after the COVID-19 pandemic began in the United States looked at initial enrollments to treatment and cancer control and prevention clinical trials conducted by the SWOG Cancer Research Network between January 2016 and February 2021.⁶ Of 29,398 patients (23,034 before the pandemic and 5364 from March 1, 2020, to February 28, 2021), a substantial decrease was seen in weekly trial enrollment from the onset of COVID-19 in late winter 2020.⁶ The rate of weekly enrollment increased from April 26, 2020, to October 3, 2020, but decreased again during the surge of COVID-19 in late 2020 to 2021, although less than the initial wave.

In March 2020, the NCI, through the NCI Cancer Therapy Evaluation Program and the NCI Community Oncology Research Program, provided interim guidance for patients on clinical trials.⁷ Guidance for Investigational New Drug (IND) and non-IND trials included allowing transfer of patient care to another site to allow for patient safety and/or comply with mandatory travel restrictions, permitting continuity of care by nonresearch staff, and consideration for shipment of oral IND agents directly to patients enrolled on clinical trials. Additional guidance was provided later in March 2020, addressing major and minor protocol deviations related to the COVID-19 pandemic, the use of telehealth for adverse event assessments, protocol-specified laboratory and imaging testing, treatment delays, and biospecimen collections.⁸ Importantly, remote informed consent was not considered a protocol deviation, and virtual remote auditing/monitoring of clinical trials could be considered via a secure access portal.

TELEHEALTH

As COVID-19 was identified as a global health threat,⁹ enrollment of NCI patients on clinical trials at the NIH CC fell substantially. It was incumbent upon investigators, regulatory agencies, and research staff to swiftly implement changes in clinical

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trial design and practice to sustain clinical research while safeguarding the health of cancer patients as well as research and clinical staff during the pandemic and beyond. The NCI quickly sought to simplify treatment schedules, facilitate telehealth, and decrease required data collection while engaging and expanding partnerships with community oncologists.¹⁰ One of the earliest adaptations at the NIH was the implementation of telehealth in clinical trial conduct. Telehealth, health care that is delivered by means of telecommunication tools,¹¹ can be utilized to access complex oncologic care while maintaining safety measures such as social distancing.¹² At the CC, the Health Information Management Department expanded the Telehealth Concierge Service to provide support services. The Telehealth Concierge services include coordinating appointment scheduling in MS Teams, providing educational materials for patients and NIH staff, contacting and educating patients about the telehealth process, conducting technical checks with patients the day before appointments, assisting with technical issues for patients and providers, and providing iPads for inpatients for telehealth visits. In April 2020, 52 telehealth appointments were conducted at the NIH. By March 2021, 1229 telehealth appointments were scheduled and conducted. From April 2020 to June 2021, 11,658 telehealth appointments were conducted at the NIH with 3973 of those NCI appointments. As federal hospital practitioners are permitted to have a license in any of the 50 states or the District of Columbia, care originating from the CC in Bethesda, Maryland, does not require a Maryland medical license, which facilitates telehealth appointments. Telehealth is also made potentially easier by the ability to treat patients without the need to involve third-party payers.

The medical community as a whole was forced to adapt quickly because of the COVID-19 pandemic, and telehealth allowed for patients to be screened for trial enrollment and limited unnecessary exposures by patients and health care workers.¹³ As seen at the NCI and at the NIH, telehealth is an important part of clinical care, and vital lessons were learned from incorporation of telehealth, particularly in clinical trials. The traditional clinical trial model has been based on limiting sites of clinical care to 1 or more academic research centers or qualified community research programs. Clinical trial participants have been limited in where they can receive care and treatment. At the NCI, the focus has become how to amend current research protocols, and implement future ones, to allow for telehealth visits, especially for follow-up visits on study. This will enable participants to travel less and have fewer visits to the NIH. It is time to reassess what data are of importance for clinical research and how to simplify that data collection. Requirements for physical examinations should be thoughtful and may not be necessary at every visit, thus allowing for more telehealth opportunities. Clinical trials can also allow for validated devices to track vital signs and relay the information to the research team. It is incumbent on clinical research teams and community multidisciplinary teams to establish close partnerships so data can flow back and forth unencumbered. If an adverse event is suspected on a telehealth visit, having a cancer care team member available in the community can facilitate prompt evaluation and help ensure the safety of participants.

An important aspect of telehealth is remote informed consent. In a pandemic, when research staff may be diverted to support pressing clinical challenges, some research staff members are working remotely, and patients are at high risk of infection, adaptability is required to ensure that vital research continues. Procedures were quickly implemented to improve operational efficiency and safety at the NIH. The NCI Central Institutional Review Board issued relevant guidance on remote consenting.¹⁴ Prior to amending the research protocols, remote consenting was considered a protocol deviation, but was permitted on an emergent basis in individual cases.

The purpose of remote consenting is to allow the investigator or designee and potential trial participant to engage in the informed consent process in a similar fashion to in-person consent.¹⁴ Telehealth was an option for consent (along with telephone, conference call, etc.). Beyond use during a pandemic, remote consenting allows for increased access for patients who cannot travel to study sites because of socioeconomic pressures or comorbidities that may limit their ability to travel.

CORRELATIVE STUDIES

Correlative studies, which can be described as the evaluation of biomarkers associated with clinical outcomes and product mechanism of action¹⁵ in the context of a clinical intervention trial, have been inherently fraught with limitations. These studies need careful and considerate incorporation into clinical trials to address specific scientific questions and for biospecimens to be batched for analysis when scientifically feasible. Blood work and biopsies have the potential to yield important information and must be carefully collected, transported, and stored to justify the risks to study participants of obtaining specimens. Again, the NCI has stressed flexibility in protocol design and management to conduct correlative studies and to decrease the number of visits needed to the NIH. With community and commercial partnerships, basic laboratory work and research specimens could potentially be obtained through community resources and shipped for further analyses. Similarly, shipping of commercial agents to trial participants throughout the country should be considered. Clinical trials can be re-envisioned to allow for intravenous study medications to be accessible at tertiary centers and community practices near a patient's home. Partnerships between physicians, sponsors, and regulatory agencies would allow for such adaptability and access.

HEALTH DISPARITIES

Women and minority populations remain underrepresented in clinical trials.¹⁶ Rural populations and participants of lower socioeconomic status are underrepresented in oncology trials.¹⁷ The quality of science and applicability of results improve with inclusion of participants who represent all populations.¹⁸ Numerous societal factors are associated with underrepresentation, but clinical investigators play a role in determining how underrepresented minorities (URMs) can participate in clinical trials.¹⁹ One strategy is broadening eligibility criteria, especially those related to comorbidities and secondary cancers. At the NCI, broadening eligibility criteria is an implementation objective of the NCI Clinical Trials Strategic Plan. Clinical trial study designs need to be simplified, as often protocol designs are unnecessarily complex without adding to scientific insight, to still achieve primary and secondary objectives.

Although the CCR covers transportation costs and provides a stipend for participants on clinical trials at NIH's main campus, the economics of traveling may still impact URMs and those of lower socioeconomic status disproportionality. In such cases, telehealth has the potential to lessen the burden via reduced travel costs. Again, working closely, and creating partnerships, with other institutions, institutional review boards, sponsors, and the Food and Drug Administration will enable successful recruitment and retention of URMs into cancer clinical trials. The intramural program also has the potential to purchase tracking devices and communication tools for patients with financial need.

Clinical trial access is limited or prohibitive for individuals from rural areas of the United States. Lack of proximity to major academic centers leads to disparities in clinical trial enrollment.²⁰ Limited bandwidth and Internet capabilities make rural communities hard to reach.²¹ Health care infrastructure, already struggling because of lack of resources, is further impacted by COVID-19.

Despite these challenges, strategies to reach these communities are available, and with flexibility and adaptation, improvements can be achieved. One such strategy is to partner state and local departments of health with private companies to increase broadband coverage.²⁰ Telehealth has proven to be important in reaching URMs and can be thus utilized in rural areas. Decentralization of clinical trials through partnerships and investments will improve care and delivery for populations that need access to oncologic research.

REGULATORY REQUIREMENTS

The modernization of regulatory requirements will enable greater clinical trial participation. Simplifying data collection to require only critical elements necessary to achieve study objectives and monitor patient safety will allow for participating sites to capture necessary elements, develop databases, and complete remote monitoring with decreased burden.²² Minor protocol deviations do not need to be collected, and adverse event reporting should be reduced when the events have no impact on patient safety. This will lead to improvement in the logistical and data quality challenges of extracting clinical trial data from electronic medical records. In addition, simplifying eligibility criteria and study endpoints potentially allows for enhanced patient access. Critical thought is needed in protocol design, correlative laboratory, and biopsy schedules, and the collection of test data needs to be clinically relevant to study endpoints.

FUTURE DIRECTIONS

Clinical trial implementation and conduct have changed dramatically at the intramural research program since the beginning of the COVID-19 pandemic. Clinical researchers rapidly responded to the pandemic by identifying impediments to clinical trial accrual and research and devising plans to address these impediments while maintaining the safety of our cancer patients. Removal of restrictive eligibility criteria and simplifying clinical trial designs and operating characteristics are initial steps toward improvement. Remote consenting has been implemented for patients to reduce travel requirements and travel burden. Oral investigational agents are mailed to patients to allow continuation of treatment without disruption. Monitoring and audits have been transitioned to virtual platforms while maintaining trial integrity. Telehealth has been implemented with the support of a concierge service for consultations and follow-up study visits. Modernization of regulatory requirements and guidance was provided to the oncologic community. Decentralization of testing and imaging studies and partnerships with regulatory agencies, academic centers, and primary providers have been sought. These changes seek to improve operational efficiency, lower barriers to trial entry, and enhance outcomes. As new variants emerge,²³ we are reminded our mission for improved cancer care continues, but the time is right to advance upon current standards. Federal institutions such as the NCI CCR have the tools and flexibility to ease the burden on our patients while increasing access to clinical trials to a greater number of patients safely and effectively.

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