Cancer Researchers Reimagine Clinical Trials Amid COVID-19 Pandemic

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Responding to Coronavirus, Cancer Researchers Reimagine Clinical Trials

When the coronavirus pandemic reached the United States, thousands of people with cancer were participating in clinical trials, including many at St. Jude Children's Research Hospital in Memphis, Tennessee.

At St. Jude, investigators took steps to reduce the risk that children participating in clinical trials, including studies testing new cancer drugs, would become infected with the virus that causes COVID-19. Limiting patient visits to the hospital was one strategy for preventing infections.

So, instead of having patients come to the hospital for routine assessments, nurses went to the patients, who were staying with their families in housing provided by St. Jude.

Teams of nurses, carrying backpacks with medical supplies and personal protective equipment, met with the children and provided basic care, such as collecting blood samples. The nurses essentially brought the clinical trials to the patients, an idea that has attracted new interest among researchers during the pandemic.

"We are very concerned about preventing our patients from being exposed to the novel coronavirus," said Robin Mutz, RN, chief nurse executive at St. Jude. Although St. Jude remained open during the pandemic, health care providers preferred that patients not come to the clinics unless necessary, she added.

Another change made by St. Jude was to begin virtual research visits between health care providers and patients, also known as telehealth or telemedicine. Some of the nurses who visited patients staying at St. Jude had been trained to help with telehealth visits.

For telehealth and virtual research visits to continue beyond the pandemic, said Mutz, some of the temporary changes that had been made to regulations on the use of telehealth during COVID-19 would need to become permanent.

A greater use of telemedicine has emerged as one of the positive changes to cancer clinical trials that could be continued after the pandemic has passed, according to the results of two surveys of clinical trial investigators and a series of recent commentaries by leaders of clinical trials.

Other changes to trials during the pandemic that could be incorporated into future studies include the use of electronic signatures for patient consent forms, remote monitoring of clinical trial results, and shipping oral medications directly to patients participating in clinical trials.

“We’ve learned some lessons,” said William Dahut, MD, who is scientific director for clinical research at NCI’s Center for Cancer Research and conducts clinical trials. “My hope is that we emerge from this period with improvements in the way we conduct cancer clinical trials.”

In the past, such changes might have been viewed as violations of study protocols. But, in March, NCI provided guidance for clinical trial activities affected by the coronavirus. The Food and Drug Administration also issued a guidance on clinical trials of medical products during the pandemic.

“We have been closely monitoring NCI-sponsored clinical trials to understand how we can make accommodations so that patients can receive care while the clinical trial investigators can, as much as possible, continue the studies,” said Meg Mooney, MD, of NCI’s Cancer Therapy Evaluation Program.

NCI has given trial sites flexibility in the operations of trials, including in the timing of when patient tests and assessments must be done.

“Investigators leading clinical trials can work with the Institutional Review Board that oversees each study protocol to make necessary adjustments,” Mooney explained. “These modifications will provide flexibility without compromising patient safety or the validity of the data being collected by the trial.”

“A Sense of Unknown”

Clinical trials are critical for progress against cancer. And trials that evaluate new therapies are often the best, or the only, treatment option for some patients. During the pandemic, NCI continued to enroll clinical trial participants for whom the NIH Clinical Center, located in Bethesda, MD, had the most appropriate treatments.

The biggest challenge in the first weeks of the pandemic “was a sense of the unknown,” said Dahut. Travel restrictions and other measures put in place to reduce the spread of the novel coronavirus raised questions about how to care for patients who travel long distances to come to their appointments. Should these patients even make the trip to Bethesda? Should their treatments be given on a different schedule, such as every 6 weeks rather than every 4 weeks?

“We were trying to find the balance between treating patients for their cancers and ensuring that the patients were safe while traveling,” he said. But the researchers had limited information to

guide their decisions, he added.

Telemedicine has helped to reduce the need for in-person visits to the Clinical Center. Patients who are taking a new drug should be seen once a week, Dahut noted, but this can often be done virtually.

“Most experienced investigators can get a pretty good sense of how someone’s doing by looking at the person during a virtual visit,” he said. Patients who are seen virtually need to be in contact with local physicians who can provide immediate medical attention if necessary, he added.

Another attractive feature of telehealth is the ability for family members who live far from a patient to participate in a conversation with doctors, noted Dahut. “Through telehealth technologies, a physician could invite a son or daughter immediately into the conversation, allowing the child to hear the discussion and see the body language of the parent,” he said.

At the same time, Dahut and his colleagues have been trying to reduce the number of required tests and patient visits to the Clinical Center without compromising patient safety and the scientific integrity of the clinical trials.

To do this, the researchers carefully evaluate each patient and consult with the Institutional Review Board and sponsor of the trial, according to a commentary cowritten by Dahut on what clinical trials might look like after COVID-19.

Surveys Provide a Snapchat of Changes in Clinical Trials

Early in the pandemic, leaders at the American Society of Clinical Oncology realized that clinical trials would be affected, so they developed a survey to capture some of these changes. Conducted in late March, the survey elicited responses from 32 investigators, including 14 who represented academic programs and 18 who represented community-based programs.

“The survey was a snapshot of what people were seeing and feeling at that time, and I think it serves as a motivator to make the necessary changes to improve the clinical research system,” said David Waterhouse, MD, of Oncology Hematology Care in Cincinnati, who co-led the survey.

“Telemedicine was probably the most widely adopted solution to the challenge of getting patients seen and making sure they were taken care of during the pandemic,” he continued.

Waterhouse noted that not every patient can travel to cancer centers for treatment and that this can lead to disparities in care. “A goal for the future is to bring clinical trials to the patient rather than making the patient come to the trial,” he said, adding that telemedicine would likely play an important role.

A majority of investigators who responded said their institutions had developed formal policies related to the COVID-19 pandemic. In three-quarters of the respondents’ programs, research staff were mandated to work remotely.

Delays in clinical research activities were common, the survey found. A majority of respondents' programs stopped cancer screening and/or enrollment for certain clinical trials, including those that were conducted for research purposes only.

"Many cancer centers began to prioritize which trials could continue to enroll patients based on the severity of the disease and the treatment options available to a patient, and also on the center's own staffing," said Waterhouse.

These findings were consistent with the results of a second survey involving 36 investigators that was conducted between March 23 and April 3. The enrollment of patients in active cancer clinical trials decreased during the survey period. In the United States and Europe, only 20% and 14%, respectively, of the institutions continued to enroll patients at the usual rate.

Clinical Trials in the Community

In the United States, the impact of the pandemic on cancer clinical trials has varied depending on the extent of COVID-19 in the areas where the studies have been conducted.

This has been seen across NCI's Community Oncology Research Program (NCORP), which conducts clinical trials at more than 1,000 sites in 43 states plus the District of Columbia, Puerto Rico, and Guam. Some are in rural areas and others are in urban centers. NCORP includes 14 sites that are designated as Minority/Underserved Community Sites.

In addition to participating in cancer treatment trials, NCORP also conducts trials in cancer prevention, screening, symptom management, and the delivery of cancer care.

At the start of the pandemic, NCORP determined that providing care for those patients who are undergoing treatment for cancer was the priority, according to Worta McCaskill-Stevens, MD, chief of NCI's Community Oncology and Prevention Trials Research Group, which includes NCORP.

NCORP provided sites with guidance on how to modify trials during the pandemic, allowing the remote signing of consent forms and virtual follow-up meetings with doctors. Patients who could not travel to their primary clinical trial sites were allowed to go to another site or to a local health care provider.

"From NCORP's diverse oncology practices, including cities and rural areas, NCI is capturing valuable information about the resiliency of community investigators during crises and about their commitment to cancer care and research," said McCaskill-Stevens.

Some rural oncology practices that were already using telemedicine relied on this mechanism during the pandemic to maintain as much of their clinical practices as possible, she noted. Some of the Minority/Underserved Community Sites in cities were more challenged by the pandemic.

"Two NCORP hospitals in New York City, Columbia and Montefiore, focused their resources on caring for people with COVID-19," said McCaskill-Stevens. "The heroic efforts of health care providers and staffs at these hospitals were widely covered by the news media."

In Chicago, she noted, the Cook County NCORP was forced to temporarily close its chemotherapy unit after members of the cancer treatment team were possibly exposed to the coronavirus.

“The pandemic has challenged the practice of oncology as we know it,” said McCaskill-Stevens.

Clinical Trials for Children with Cancer

Like the NIH Clinical Center and other clinical trial sites, St. Jude has continued to enroll patients who have few treatment options, such as children with brain tumors or other aggressive cancers, on clinical trials of new therapies.

But the hospital temporarily stopped enrolling new patients on clinical trials that do not evaluate a treatment, including trials related to cancer prevention and survivorship, according to Elizabeth Fox, MD, who oversees clinical trials research at St. Jude.

Another way that St. Jude tried to prevent the spread of COVID-19 was to request that only one family member or guardian accompany each child to the hospital during visits. “The one caregiver policy has been necessary, and we recognize that it is a sacrifice for families,” said Fox, noting that St. Jude treats patients with cancer from across the United States.

“For any family, a diagnosis of childhood cancer can be enormously stressful,” she continued. “The pandemic has only added to the uncertainty that these families were already experiencing.”

With a smaller staff at the hospital, some of the standard assessments for children on clinical trials of new treatments had to be delayed. “Some families understandably began to wonder whether their children would be able to receive their treatments on schedule and then learn whether the treatments were effective,” said Fox. “This was another source of stress.”

Researchers at St. Jude have also begun to ship oral drugs directly to the families of patients testing these medicines, sparing them a trip to the hospital. “This is something we’d like to continue in future trials of oral drugs,” said Fox.

Monitoring Clinical Trials

Clinical trials are monitored to assure the quality of the data being collected by researchers and compliance with regulations for clinical research. Before the pandemic, monitors would typically travel to trial locations and use on-site computers to review data from the studies, such as patient electronic medical records (EMRs).

In response to the pandemic, however, NCI’s Cancer Therapy Evaluation Program has begun to adopt remote approaches to monitoring studies.

“Before COVID-19, only a handful of institutions running NCI-sponsored trials would allow auditors to access EMRs remotely,” said Gary L. Smith, who leads NCI’s Clinical Trials Monitoring Branch, which sets guidelines and standards for the conduct of NCI-sponsored clinical trials. “But we are definitely seeing more and more remote audits.”

Now that most medical records are electronic and can be accessed from a computer anywhere, “it doesn’t make sense to me to have monitors traveling to sites,” Smith said. “I don’t think we can completely replace on-site audits, but I think we can augment these audits with remote monitoring approaches.”

Some sites have recently been allowing auditors to visit in person, he noted. But trial sites have set up facilities within their institutions that are apart from patients to reduce the possible spread of COVID-19.

“Our main concern,” Smith said, “has always been the safety of the monitors who have to travel to the sites and the safety of patients in trials who might be exposed to the coronavirus by an asymptomatic but infected monitor.”

Expanding the Reach of Clinical Trials

Travel to clinical trial sites has been a longstanding burden for some patients participating in clinical trials and may contribute to disparities in who is served by these studies, noted Eric J. Small, MD, who studies and treats patients with prostate cancer at the University of California, San Francisco.

But the pandemic has created an opportunity to review current practices in cancer clinical trials, including how frequently patients in certain trials need to be seen for in-person assessments, Small wrote in a commentary on the urgent need for transformation in cancer clinical trials.

“We’re learning that we can do a lot more remotely than we might have thought,” Small said. “Obviously, there are some situations where we have to see the patient, but I think we have learned that having the flexibility of being able to use telemedicine is important.”

He added, “We’ve also learned that assessing the patient’s response to treatments every 6 weeks might be a little too often and that nothing is lost by doing it every 3 months.”

During the pandemic, Small and his colleagues at UCSF dramatically changed their approach to treating patients with cancer, including those in clinical trials. Care decisions were driven, he explained, by whether a health care professional deemed a patient’s treatment essential. Such patients continued to come into the hospital and to enroll on clinical trials.

San Francisco has not been hit as hard as cities on the East Coast by the pandemic, and the UCSF Helen Diller Family Comprehensive Cancer Center is “in recovery mode,” said Small. “Most of our clinical trials, including those high-risk, in-patient trials that were placed on hold, are again open and accruing.”

He is optimistic that, in the coming months and years, the lessons learned during the pandemic will lead to changes, such as the expanded use of telemedicine, that make trials more accessible to people “who don’t have the means to get in the car and drive all day to an appointment.”

He added, “My hope is that we can be more broadly inclusive to serve underserved populations, particularly people in rural areas.”

Delays in Diagnosis

Investigators at St. Jude and elsewhere have found that fewer childhood cancers have been diagnosed in recent months compared with previous years. But this is not necessarily good news. “We know that childhood cancer is out there,” said Fox.

The likely reason for the declining numbers is people have not been going to the doctor as often as they did before the pandemic. Delays in diagnosis could lead to an increase in cancers in children that are detected at more advanced stages. Advanced cancers are more difficult to treat than early-stage cancers, she added, and often require more aggressive treatments, which tend to have more short- and long-term side effects.

There are similar concerns about adult patients, according to McCaskill-Stevens. “The entire cancer community is concerned about delays in diagnosis as a result of the pandemic,” she said.

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