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Early Impact of COVID-19 on the Conduct of Oncology Clinical Trials and Long-term Opportunities for Transformation: Findings from an American Society of Clinical Oncology Survey

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ABSTRACT

The COVID-19 pandemic has disrupted all aspects of clinical care, including cancer clinical trials. In March 2020, the American Society of Clinical Oncology launched a survey of clinical programs represented on its Cancer Research Committee and Research Community Forum Steering Group and taskforces to learn about the types of changes and challenges that clinical trial programs were experiencing early in the pandemic. There were 32 survey respondents; 14 represented academic programs and 18 represented community-based programs. Respondents indicated that COVID-19 is leading programs to halt or prioritize screening and/or enrollment for certain clinical trials and cease research-only visits. Most reported conducting remote patient care where possible and remote visits and monitoring with sponsors and/or contract research organizations; respondents viewed this shift positively. Numerous challenges with conducting clinical trials were reported, including enrollment and protocol adherence difficulties with decreased patient visits, staffing constraints, and limited availability of ancillary services. Interactions with sponsors and CROs about modifying trial procedures were also challenging. The changes in clinical trial procedures identified by the survey could serve as strategies for other programs attempting to maintain their clinical trial portfolios during the COVID-19 pandemic. Additionally, many of the adaptations to trials made during the pandemic provide a long-term opportunity to improve and transform the clinical trial system. Specific improvements could be expanded use of more pragmatic or streamlined trial designs, fewer clinical trial-related patient visits, and minimized sponsor and CRO visits to trial programs.

INTRODUCTION

The Coronavirus (SARS-CoV-2) and the resulting Coronavirus Disease 2019 (COVID-19) have disrupted all aspects of clinical care in the United States and around the world. Patients with cancer constitute a vulnerable population and are at a high risk of contracting and suffering adverse consequences from the disease.[1-4] Oncology providers are focused on limiting exposure of their patients and patients' caregivers to people with COVID-19 and asymptomatic carriers of SARS-Cov-2, while continuing to ensure access to needed cancer treatment and clinical trials. Providers are also concerned about protecting themselves, their families, and their staff from COVID-19.

One area of cancer care that has been especially disrupted by COVID-19 is the conduct of clinical trials. The disease has the potential to impact the scientific integrity and patient safety of ongoing trials;[5,6] increase operational burdens on trial programs; and limit access to trials and newer therapies for all patients, especially the most vulnerable populations. Issues related to scientific integrity stem from the need for sponsors and trial programs to maintain compliance with good clinical practice during the pandemic. Trial programs may be unable to meet all of the protocol specific requirements and procedures, such as protocol mandated tumor biopsies, outpatient visits, laboratory/diagnostic testing including imaging, and completion of patient questionnaires. This may lead to protocol modifications and/or deviations (intentional or unintentional) with unknown consequences.[6] Trial programs are also facing challenges with maintaining their clinical trial portfolios while providing essential clinical care and operating under reduced financial resources and smaller staff. Many programs are modifying their approach to patient encounters to prevent patient and staff exposure to COVID-19 and to comply

with existing regulations and public health guidance. Altogether these modifications and new burdens on programs are likely to negatively affect patient accrual to trials.

Regulatory and research organizations have issued guidance and developed new policies and procedures to address the safety and scientific challenges to conducting clinical trials in this environment. The U.S. Food and Drug Administration (FDA) and international regulatory agencies released guidance to industry, investigators, and institutional review boards (IRBs).[6,7] The National Cancer Institute (NCI) and the National Institutes of Health (NIH) also released guidance about clinical trial activities affected by COVID-19.[8] Additionally, other research-focused, philanthropic, and advocacy organizations have launched initiatives related to COVID-19 and the conduct of clinical trials. For example, the Clinical Trials Transformation Initiative (CTTI) collected feedback from various stakeholders related to the FDA guidance and hosted a webinar that identified emerging best practices in conducting clinical trials during this time.[9]

The American Society of Clinical Oncology (ASCO) is committed to providing current information and resources about COVID-19 to oncology providers and the larger oncology community. ASCO has developed online resources; hosted webinars; created online forums for discussion, including a forum for sharing research specific challenges and strategies; and provided patient-oriented information.[10-12] It published recommendations for the allocation of scarce resources while providing care during the pandemic.[13] On April 10, 2020, ASCO also launched the ASCO Survey on COVID-19 in Oncology (ASCO) Registry to help the cancer community learn more about the patterns of symptoms and severity of COVID-19 among patients with cancer, as well as how COVID-19 is impacting the delivery of cancer care and patient outcomes.[14]

On March 24, 2020, ASCO launched a survey of clinical programs represented on its Cancer Research Committee and Research Community Forum Steering Group and taskforces to learn about the types of challenges and changes to clinical trials that research programs were experiencing due to the COVID-19 pandemic. The survey results provide an early snapshot of the clinical trial environment across a variety of types of U.S. research programs. The leadership of ASCO's research-oriented committees also believes the survey identified some changes in practice that provide long-term opportunities to transform clinical trials, refine existing research infrastructure and procedures, and promote patient-centered research. This paper summarizes the key findings from the survey, provides strategies for modifying the conduct of clinical trials during the pandemic, and identifies several long-term opportunities for transforming trials.

KEY SURVEY FINDINGS

ASCO sent the survey to 64 individuals at U.S.-based research programs via an open SurveyMonkey link that was available March 24 to March 30, 2020. A detailed report of the survey findings is available on ASCO's website.[15] Recipients were instructed to forward the survey to a colleague in their program for completion if that person had more familiarity with COVID-19-related clinical trial policies and procedures.

ASCO received 46 responses (71.9% response rate), 14 of which were substantially incomplete and excluded from analysis. Data from 32 surveys were included in this analysis. While duplicate responses from a single program are unlikely, survey results were submitted anonymously and thus uniqueness by program cannot be confirmed. Forty-four percent of respondents represented academic clinical trial programs (n=14) and 56% represented community-based programs (n=18). The survey was completed by 15 individuals who identified as a Research Director, Administrator, or Manager (Clinical/Non-Clinical) (46.9%), 14 who

identified as a Physician Investigator or Medical Director (43.8%) and 3 who identified as Research Staff (Clinical and Non-Clinical) (9.4%).

Research Program Policies and Priorities

A majority (64%) of respondents reported that their institutions had developed formal policies related to the COVID-19 pandemic. Most described implementing remote patient care interactions where possible, such as patient review of symptoms (90.6%) and telehealth visits (87.5%). Three-quarters of programs mandated remote work by their research staff. Many program policies were directed specifically at clinical research operations. Remote site initiation visits (65.6%) and remote monitoring by sponsors and/or contract research organizations (CROs) (71.9%) were common. Delay of clinical research activities was also prevalent: nearly 60% of respondents' programs halted screening and/or enrollment for certain clinical trials (59.4%) and ceased research-only visits except those providing cancer treatment (59.4%). Half of respondents reported ceasing research-only blood and/or tissue collections.

Over fifty percent of programs reported prioritizing enrollment for certain clinical trials (53.1%) and respondents shared specific trial prioritization strategies used at their programs. These strategies included a tier-based approach to prioritizing trials based on patients' needs, safety, and disease severity; potential patient and site burdens; and availability and allocation of program resources. NCI-funded cancer care delivery research and prevention/control trials were also halted per NCI guidance.[8]

Challenges to the Conduct of Clinical Trials

Respondents reported numerous challenges with conducting clinical trials as a result of the COVID-19 pandemic. Over half of the respondents observed a decrease in patient ability or

willingness to come to their site (54.8%) and cited the staff time needed to organize, implement, and conduct telehealth visits as a significant challenge. About half of respondents noted that limited availability of ancillary services (e.g., radiology, surgery, cardiology, etc.) (51.6%) was challenging. Time spent in discussion with sponsors, CRO's, and IRBs about modifying trial procedures also presented a challenge for about half of respondents (51.6%). ASCO heard anecdotally that many of these discussions are stemming from duplicative, inconsistent, and variable communications from industry sponsors and CROs who were sending trial programs study-specific and company-wide messages.

Opportunities to Improve Clinical Trials

Despite the challenges associated with implementing changes to the conduct of clinical trials during the pandemic, respondents identified numerous opportunities to improve clinical trials post-COVID-19. Nearly all respondents (90.3%) identified telehealth visits for participants as a potential improvement to clinical trial conduct and more than three-quarters (77.4%) indicated that remote patient review of symptoms held similar potential. Remote site initiation visits and monitoring by sponsors/CROs were viewed positively by 71.0% and 64.5% of respondents, respectively. Slightly fewer than half of respondents (45.2%) cited remote safety lab collections as a potential opportunity for improved clinical trial operations. Other opportunities identified by respondents included: improved efficiency during study launch and enrollment (e.g., enhanced electronic IRB communications and responses, remote consenting[16]); remote patient care (e.g., shipping oral drugs directly to patients, remote adverse event assessments, and patient review of symptoms); flexibility with drug and specimen distribution, management, and documentation for transportation; and streamlined data collection, including decreased collection of "unnecessary data." Increased remote work by research staff was noted

as an opportunity to improve job productivity, satisfaction, and staff retention, as well as mitigate space issues at sites.

While the survey reflects a small sample of research programs in the United States during a rapidly changing situation, the results provide insight into the state of clinical trials across a range of types of research programs in the early weeks of the COVID-19 pandemic. Solutions and opportunities identified by these respondents may serve as useful guidance for other programs during this time of crisis and provide longer-term strategies for how to make the clinical trial programs more patient-centered and efficient moving forward.

STRATEGIES FOR CONDUCTING CLINICAL TRIALS DURING THE COVID-19 PANDEMIC

The ASCO survey results indicate that the COVID-19 pandemic is having an impact on the conduct of clinical trials. Survey respondents stated that their programs are uncertain about their near- and long-term ability to provide care with limited staff to conduct trials and with fewer available participants. Adaptations to clinical trial practices during the pandemic are critical to ensuring patient access to both ongoing and new study treatments. Clinical trial programs should follow guidance on conducting clinical trials during the pandemic from the FDA[6], NCI[8], ASCO[10], and others. Programs should also consider adopting, if not done already, the following high-level strategies to facilitate adjustments and documentation during the pandemic:

- Keep participants informed about changes to trials and their care and remind participants to alert their research team about changes to their health
- Develop formal COVID-19 standard operating procedures for clinical trials that could be repurposed with other disease outbreaks

- Leverage e-signatures for informed consent and other study documents
- Organize daily staff "huddles" to provide updates and discuss operational challenges
- Promote telehealth visits for patients
- Implement patient review of symptoms and adverse events (e.g., through patient portal, email, phone, video)
- Establish a system for prioritizing clinical trial resource allocation (e.g., determine which trials to maintain screening and enrollment)
- Require remote study initiation visits and monitoring from trial sponsors and CROs
- Use remote safety lab collections, where feasible
- Ship oral drugs directly to patients
- Communicate any changes or concerns about existing trials to IRBs
- Ensure thorough documentation of changes to procedures and modifications to or deviations from protocols, and use a "COVID-19" tag to facilitate searching after the pandemic

Many of these changes have the advantage that they will make clinical trials more patient-friendly and reduce the time and expense of participating in clinical trials.[17,18]

Additionally, the cancer research community should monitor and assess the impact of the pandemic on access and recruitment to clinical trials of racial and ethnic minorities, rural communities, older adults, and other underserved groups. Early reports indicate that COVID-19 is disproportionately impacting African American and other minority communities;[19] strategies will be needed to ensure disparities in clinical trial participation are not exacerbated further during the crisis.

LONG-TERM OPPORTUNITIES TO TRANSFORM CLINICAL TRIALS (POST-COVID-19)

The COVID-19 pandemic has led to many operational efficiencies in the conduct of clinical trials, as identified in the survey, FDA guidance,[6] and adaptations from trial sponsors and CROs. These changes were necessitated by the current environment and the need to ensure the safety of patients, clinical researchers, and staff. However, there is an opportunity to make some of these changes permanent improvements to clinical trials.

One of the early lessons has been that it is possible to conduct more streamlined or pragmatic trials. Many trials currently include tests, procedures, and strict data collection requirements and windows for assessment that are intended to maximize knowledge gained but may prove burdensome for both patients and trial programs. During the COVID-19 pandemic, some of these common requirements have not been able to be met, leading to protocol modifications and/or deviations (intentional or unintentional). The research community should evaluate the impact of these protocol modifications or deviations on the scientific integrity, interpretation, and conclusions of trials. It is likely that many trials moving forward could be designed with expanded and/or flexible timelines and reduced data collection requirements without negative consequences. This would be beneficial to patients and research programs.

Another lesson from the COVID-19 pandemic is that trials could routinely leverage technology to limit in-person visits for trial programs and patients. Many industry sponsors and CRO visits and oversight (i.e., feasibility assessments, site initiations, monitoring) are being conducted remotely, or in some instances, eliminated altogether during the pandemic. Given that trial activity is able to continue, many of these in-person visits should not be required post-COVID-19; virtual visits and a centralized, risk-based approach to monitoring (as encouraged in

guidance from the FDA)[20] should be sufficient. E-signatures for trial documents should also become standard practice. Similarly, patient visits during the pandemic are being minimized and should continue to be limited after the pandemic. Strategies for achieving this include the use of secure telehealth technology, patient review of symptoms and adverse events, and remote consenting, as well as making many exploratory or research-only assessments voluntary (e.g., biopsies, radiographic studies, other exams). Pharmacies could also continue to ship oral therapies directly to patients, rather than require pick-up, and local oncologists at nonresearch sites could routinely provide safety assessments rather than require patient visits to research sites.

CONCLUSIONS

The COVID-19 situation is changing rapidly. This is an overwhelming and uncertain time for patients, oncology care providers, research staff, trial programs, trial sponsors, and CROs. The results of ASCO's survey and other reports from the research community suggest that clinical trials are being impacted. It is crucial that ASCO and other research organizations continue to monitor the situation, collect feedback from stakeholders, and identify effective strategies for navigating the evolving situation. At the same time, study sponsors, research programs, and regulatory agencies should recognize that protocol modifications and deviations are inevitable and should be documented and reported. The most important consideration for trial programs during these uncertain times should be to ensure the safety of patients, providers, and research staff.

The leadership of ASCO's research committees also urges all stakeholders in the research community to seize this opportunity to make permanent the positive adaptations to clinical trials that they introduced during this pandemic. Specific improvements may include expanded use of more pragmatic and streamlined trial designs and protocols, a reduction in clinical-trial related

in-person patient visits, and minimized sponsor and CRO visits to trial programs. Capitalizing on this moment will require support from federal regulatory and research agencies, sweeping policy changes by sponsors and CROs, and widespread buy-in from the clinical trial community that there is a need to simplify the conduct of clinical trials. These changes are critical to improving clinical trials and providing a robust evidence base for the treatment of cancer. ASCO will continue to advocate for policies that support a robust clinical trial system and ensure that every patient with cancer has access to high-quality, affordable care.[21]

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