Virtual Clinical Trials in Oncology—Overview, Challenges, Policy Considerations, and Future Directions

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COVID-19 has proven to be a transformational event for medicine in the 21st century, driving rapid multisectoral change (eg, care provision via telemedicine and site-of-care optimization) and creating new value propositions for healthcare systems worldwide. The potential for such change is especially apparent in the clinical research enterprise, which has long been characterized by high costs, lengthy timelines, and nonrepresentative study populations. The challenges are particularly pronounced in oncology trials because of factors ranging from illness severity (including risk of immunosuppression), travel burden, therapeutic diversity, and regulatory complexity. Consequently, pandemic-era policy changes and delivery innovations—from regulatory flexibilities for telemedicine use to home deliveries of investigational products—provide a window to accelerate the decentralization and digitization of clinical trials. In this article, we outline an oncology-specific paradigm for virtual clinical trials, identifying the key components for study design and describing the challenges and regulatory considerations for patients, providers, and policymakers.

Framework for Virtual Clinical Trials in Oncology

Traditional clinical trials are limited by high costs (because of site-of-care restrictions and staffing needs), poor accessibility (because of geographic location), and significant participant burden (because of in-person study requirements). Studies that eschew this approach in favor of more inclusive, patient-centered study designs are characterized by the use of digital technology to streamline different study elements (eg, electronic enrollment) and site-of-service flexibilities to increase the accessibility and convenience of trials (eg, telemedicine for study visits).[1,2] For the purposes of this article, we will follow the nomenclature of the National Academy of Medicine and use virtual clinical trials as the umbrella term for studies using these flexible and technology-enhanced elements.[3] It is important to acknowledge that such nomenclature has both semantic and substantive limitations for clinical research broadly and in oncology specifically, where in-person interaction is necessary for many study components including advanced imaging of tumors and chemotherapy infusions. However, as expert panels have noted, the term virtual itself can help convey the overall paradigm shift for trial design. Additionally, although elements of the virtual trial paradigm may be applicable to all phases of clinical research, we acknowledge that the complexity and clinical risk in phase I trials in oncology may limit the use of discrete elements (eg, digital technologies), and consequently in this editorial, we will use examples from late-stage trials to illustrate the value proposition for cancer research. In Figure 1, we delineate the oncology-specific challenges and virtual trial use cases at each stage of the clinical trial workflow.

Leveraging advanced analytics to enhance recruitment. The first bottleneck for studies is recruitment, which represents the single largest cost-driver for clinical trials and accounts for 30% of failures in phase III studies.[4] The poor participation rates in oncology trials (2%-8% of all patients with cancer), despite favorable public opinion, largely stem from a supply-demand mismatch; trials are generally unavailable at cancer treatment facilities beyond academic medical centers in urban settings, and patients are frequently ineligible for studies.[5]

Under a virtual paradigm, investigators can leverage digital technologies to streamline recruitment, reduce administrative costs, and improve inclusion (Fig 2). For example, cancer centers are beginning to leverage artificial intelligence (AI) for patient-trial matching. These platforms use natural language processing and other AI techniques to ingest patient information contained in both structured and unstructured elements of the electronic medical records, discern eligibility, and match patients to relevant open trials in the ClinicalTrials.gov database.[6,7] The value of these advanced analytics platforms in oncology will undoubtedly increase as regulators seek to broaden historically restrictive eligibility criteria (eg, exclusion of patients with HIV and patients with prior cancer) and as investigators increasingly use specific biomarkers to guide therapy selection (eg, tumor mutational burden for immunotherapy).[8]

Using electronic tools to streamline enrollment. A substantial proportion of eligible patients will not enroll

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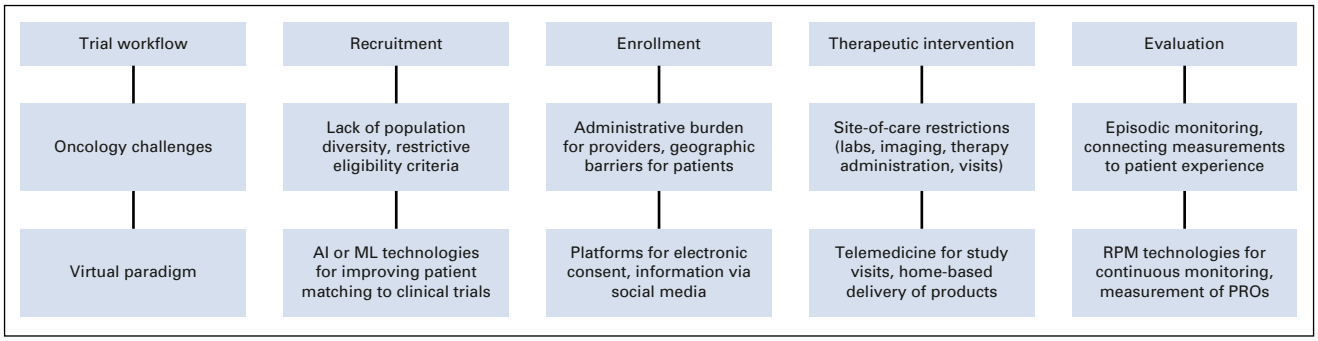

FIG 1. Framework for virtual clinical trials in oncology. The top row depicts the key elements of a clinical trial; the middle row outlines oncology-specific challenges in clinical trials; and the bottom row identifies examples of solutions in a virtual paradigm. AI, artificial intelligence; ML, machine learning; PROs, patient-reported outcomes; RPM, remote patient monitoring.

in clinical trials because of structural (eg, administrative burden) and attitudinal factors (eg, misinformation and historic distrust of the health system). Under a virtual model, investigators can use electronic tools to streamline different enrollment processes. In addition, virtual trial conduct enhances the ability for centralization of trial conduct and oversight, markedly reducing both study site activation times and costs. The US Food and Drug Administration (FDA) has previously issued guidance on obtaining informed consent via electronic platforms and has promoted the use of the agency-developed MyStudies mobile application for obtaining consent during the pandemic.[9]

Within the oncology context, studies have found electronic consent platforms to have high completion and low error rates.[10] As an example, consider an ongoing observational study at MD Anderson (ClinicalTrials.gov identifier: NCT04169542) examining the burden of out-of-pocket healthcare costs in breast cancer surgery. Investigators used electronic platforms such as REDCap to obtain informed consent.[11] They also determined patient communication preferences upfront (eg, e-mail *v* SMS text messaging), which enabled the automation of both survey deployment and notifications for subsequent study components (eg, delivery of post-operative survey and provision of incentive upon study completion). By removing the number of in-person visits needed for enrollment, investigators can lower the trial cost structure and barrier to entry for participation for underrepresented populations, particularly those with mobility limitations (eg, elderly adults and disabled patients). Furthermore, the use of this fully decentralized study design enabled investigators to continue trial operations—which spanned multiple institutions across several states—with minimal interruption during the COVID-19 pandemic.

Decentralizing study touchpoints to increase convenience for patients. Oncology trials place a uniquely high burden on participants because of site-of-service restrictions on accessing investigational products and the number of study clinic visits required for data collection. For example, in-person data collection (such as follow-up surveys) often has to be completed on site, adding to the burden of time spent in clinic while patients may not feel well while receiving cancer treatment. However, during the pandemic, regulators granted flexibilities and investigators adapted many processes to limit infection risk. First, to reduce exposure to COVID-19, investigators for oncology trials increasingly leveraged telemedicine (82%) and alternative study locations (73%) during the pandemic.[12] Given that many patients—particularly racial and ethnic minorities—cite distance from clinical sites as a major barrier to trial participation, the use of technology or hub-and-spoke models to decentralize trial operations could drive meaningful improvements in accessibility and representation.[3]

Second, the FDA guidance outlined considerations for home-based delivery of investigational products, and 64% of investigators reported an intent to ship oral drugs directly to patients in oncology trials.[12,13] The implications extend beyond the pandemic because of the growing prominence of Hospital at Home models for oncology, which allow for home-based administration of chemotherapeutic agents.[14] Although home-delivery of oncologic drugs faces challenges including proper storage, use, and security, AI platforms can provide chain-of-custody assurances and opportunities to support medication dosing and remote data collection, which in turn could provide important real-world insights into product efficacy.[15]

Broadening the evidence base through digital data collection. During the pandemic, the locus of research shifted away from study clinics and toward the home, prompting investigators to explore new avenues for data collection. For example, the FDA issued a guidance that temporarily expanded access to noninvasive medical devices for remote patient monitoring (RPM) (eg, electrocardiographs and spirometers). In oncology specifically, investigators have modified the frequency of assessment (eg, imaging) and method of sample collection (eg, home-based blood draws).[16]

These pandemic-era innovations align with the virtual trial model, which seeks to improve the capacity of studies to

FIG 2. Virtual clinical trials in oncology: where we stand and where we are headed. FDA, US Food and Drug Administration.

measure patient-reported outcomes and generate real-world evidence.[17] For example, expanded access to RPM technologies will also enable the shift from episodic to continuous measurement in clinical research, which can improve the characterization of the long-term toxicity profiles of chemotherapeutic agents and provide real-time data about their side effects. Additionally, digital tools have been demonstrated to improve the assessment of quality of life and the detection of adverse events in oncology trials.[18] These patient-reported outcomes are of increasing interest to regulators, with the FDA launching Project Patient Voice to collect patient experience data for cancer trials. For example, the symptoms measured in the reference study of platinum-based doublet chemotherapy for non–small-cell lung cancer (eg, acne development and nail color change) are easily amenable to digital measurement.[19] Consequently, the virtual trials framework can promote alignment between investigators and regulators, support the identification of new digital biomarkers, and enhance the salience of trial outcomes for patients.

Challenges and Policy Considerations for Virtual Trials

Before the pandemic, the FDA announced its intent to publish guidance on both decentralized clinical trials and the use of digital technologies for RPM during 2020. COVID-19 has accelerated the impetus for change, serving as an unprecedented natural experiment for innovation across the healthcare ecosystem. The experience from oncology trials during the pandemic will provide important insight about the safety of protocol modifications (eg, delays in clinical visits and reductions in diagnostic tests and imaging) and the receptivity of patients and providers to new trial methodologies (eg, use of virtual visits and RPM technologies). Consequently, it will be necessary for policymakers and practitioners to collaborate to identify lessons learned from COVID-19 and formalize best practices into official guidance.

First, regulators must provide clarity about which flexibilities from the pandemic will remain and which policies will be allowed to expire. Many of the innovations during the pandemic (eg, use of telemedicine and home-based delivery) were prohibited before COVID-19 because of regulatory restrictions (eg, state-based licensing laws). The Department of Health and Human Services should convene a working group with agency representatives from the FDA, Centers for Medicare & Medicaid Services, and National Institutes of Health, and experts in oncology clinical trials from the ASCO, American Association for Cancer Research, and the National Academy of Medicine, to review the flexibilities for trial conduct during the pandemic, and accordingly update federal guidance. Importantly, given the increasingly globalized nature of clinical research, the FDA should also partner with its counterparts in other countries to foster international harmonization. For example, the European Union's Innovative Medicines Initiative recently launched a Trials@Home consortium to broaden the evidence base for remote trials.

Second, as trials increasingly shift from institutional to home- and community-based settings, policymakers must ensure that the appropriate governance framework and protections are defined for patient privacy and safety. For example, the increasing use of digital technologies for passive data collection should be accompanied by clear protocols for obtaining informed consent from trial participants. Additionally, policymakers may need to clarify the scope of the Health Insurance Portability and Accountability Act as the line blurs for medical devices with both consumer and research applications (eg, Apple Watches).[3] Furthermore, given growing reports about the vulnerability of medical devices to breaches (eg, hacking), policymakers must ensure that expanded access to devices for RPM occurs in tandem with investments in cybersecurity protections.

Third, regulators and investigators should recognize that simply shifting from traditional studies to virtual trials will be insufficient to mitigate disparities in clinical participation, which are a function of systemic inequities within the healthcare system writ large. For example, although telemedicine use has increased during COVID-19, the growth in utilization among Black patients continues to lag behind White patients.[20] Millions of Americans also continue to lack access to high-speed broadband (digital divide), which may constrain the participation of rural and low socioeconomic status communities in virtual trials. Given the persistent disparities in cancer death rates along racial and geographic lines, addressing disparities in oncology trial participation is a moral imperative. Policymakers will need to invest in technical infrastructure to mitigate the digital divide in clinical research. Furthermore, investigators should seek to partner with faith- and community-based organizations to improve outreach to and enrollment of underrepresented populations in clinical trials.

In conclusion, COVID-19 presents a watershed moment to transform clinical research. Evidence on the use of pandemic-era innovations (eg, digital health technologies) and operational practices (eg, decentralized delivery) will form the foundation of the new era of oncology trials. Proactive engagement with investigators and support from regulators is needed to create the infrastructure for virtual trials. By advancing the use of digital technologies and decentralized methodologies, researchers can meaningfully improve the accessibility and quality of oncology trials.

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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