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VIRTUAL TRIALS: HOW COVID-19 HAS TRANSFORMED CLINICAL RESEARCH

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ABSTRACT

Clinical trials play a crucial role in assessing the safety and effectiveness of new medical treatments, devices, and healthcare interventions. Traditionally, these trials involve a series of in-person visits for eligibility checks, participant enrollment, administering interventions, collecting data, and conducting follow-ups—steps often requiring direct interaction between participants and researchers. However, the COVID-19 pandemic, and the resulting need for social distancing to limit virus spread, disrupted this model, causing many trials to suspend in-person activities except when essential for life-saving research. Despite these obstacles, clinical research continued as study teams swiftly adapted to virtual methods, allowing key trial activities to proceed remotely. This report focuses on the rapid shift to virtual practices within Clinical and Translational Science Awards (CTSA) centers and outlines key factors for further development. Looking to the future, a blended approach that combines virtual activities with necessary in-person visits is likely to become more common in clinical trials. While certain aspects of research will still require face-to-face interaction, future trial designs will need to incorporate remote options wherever possible.

KEYWORDS: Clinical trials, virtual visits, remote methodologies, COVID-19, social distancing, hybrid approach, in-person visits.

INTRODUCTION

Clinical trials are essential for assessing the safety and effectiveness of new drugs, medical devices, and health interventions. They are critical in developing new treatments and improving ways to prevent and manage diseases. Typically, clinical trials involve several steps: assessing participant eligibility, enrolling those who qualify, administering treatments, collecting data, and conducting follow-ups. Most of these activities usually happen face-to-face, with researchers meeting participants to perform tasks such as checking vital signs and collecting lab samples. The COVID-19 pandemic, however, brought a significant shift in how clinical trials are conducted. Due to social distancing, many research teams had to switch to virtual methods for some parts of their studies. Early in the pandemic, most in-person visits stopped, except for those required for life-saving research. Still, researchers had to find new ways to continue supporting participants already enrolled in studies. This meant coming up with alternative ways to distribute study medications, complete safety checks, and perform essential study tasks, all while meeting ethical standards, regulatory requirements, and financial constraints. Although the pandemic accelerated the adoption of remote technology in clinical research, the potential of these tools was recognized well before COVID-19. Researchers have been exploring digital methods as a way to streamline clinical studies for some time.[1],[2]

Advances in technology offer ways to make clinical trials more efficient and cost-effective while potentially bringing in more diverse participants. Traditionally, many people face barriers to participating in clinical trials, such as living far from research sites or having difficulty with mobility or time constraints. These challenges can make it hard for researchers to recruit participants who represent a variety of backgrounds, limiting the diversity of studies. Digital tools and remote options, if applied carefully to avoid widening the digital divide, could provide a more convenient experience for participants, reducing burdens like travel and missed work or school, which are factors that often contribute to trial dropout rates. By making trials more accessible,

these technologies could also help attract participants from underserved communities.

This paper discusses how virtual visits and related methods are now being used in clinical research and explores key factors to consider for future development toward a more decentralized or hybrid model of trials. The insights in this paper are drawn from a survey conducted across Clinical and Translational Science Award (CTSA) sites and the authors' own experiences managing these new approaches in their research.[2]

Impact of COVID-19 on Research Operations

The Center for Leading Innovation and Collaboration (CLIC) survey team developed a survey for Clinical and Translational Science Award (CTSA) hubs to gather insights on how these hubs adapted to the COVID-19 pandemic. This survey aimed to collect information on various adjustments, including virtual visits, informatics, biorepositories, IRB procedures, safety measures for research staff, prioritization of COVID-19 studies, and other adaptations. The survey team worked closely with writing groups to refine questions, and each hub's principal investigator (PI) was asked to submit one survey response by October 15, 2020. To ensure comprehensive input, PIs could gather expert insights from their teams through a Word document version of the online survey.

The survey received a high response rate, with 60 out of 65 hubs participating (92.3%). Most hubs (82%) reported disruptions in their research activities starting between January and March 2020. Out of the 60 responses, 58 hubs provided details on virtual visits, with 97% (56 hubs) adopting virtual methods for at least some aspects of their research. However, 3% (2 hubs) reported not adopting virtual methods due to barriers such as limited access to technology, financial constraints, institutional policies, or regulatory issues.

For essential research activities, CTSA hubs evaluated whether in-person visits were required or if these could be partially or fully conducted virtually. Virtual visits allowed ongoing participation in trials without exposing participants to COVID-19 risks. Many hubs used existing but rarely utilized remote options to support recruitment, screening, and enrollment, including phone and video calls. This shift required collaboration with study sponsors and IRBs to approve any protocol changes, and telehealth platforms like Doxy.me, WebEx, Zoom, and FaceTime were commonly used for virtual screening.[3]

Informed Consent During COVID-19

During the COVID-19 pandemic, the FDA issued guidance to help clinical trial sites adapt their processes while ensuring compliance with Good Clinical Practice (GCP). This guidance allowed for more flexible options in obtaining informed consent to reduce face-to-face interactions, especially when digital methods were not available. This flexibility enabled many sites to adopt virtual informed consent methods quickly, ensuring participant safety and compliance with regulations.

Shift to eConsent Platforms

Many Clinical and Translational Science Award (CTSA) sites transitioned from paper-based consent to HIPAA-compliant electronic platforms, like Doxy.me and REDCap, for obtaining informed consent. The survey results showed that 12 CTSAs (20%) used the REDCap eConsent platform, while 11 (18%) used REDCap without specifying the eConsent module, and 9 (15%) adopted eConsent without mentioning the platform. Vanderbilt University shared its REDCap eConsent validation materials with other CTSAs to help them implement an FDA-compliant system quickly. For sites that couldn't immediately validate their systems for FDA's Part 11 compliance, some study sponsors provided other eConsent platforms to streamline the process. Additionally, the FDA released the COVID-19 MyStudies App at no cost, enabling sites to use an FDA-approved platform. However, each of these digital consent systems required careful vetting by the institution's IT and cybersecurity teams, along with approval from the IRB.[2],[3]

Temporary Nature of FDA Flexibility

The FDA's flexibility under the Public Health Emergency declaration, however, is temporary. Once the emergency ends, the guidelines may change, so clinical researchers will need to plan for consent options, including virtual methods, in future study designs. This consideration is especially important for cases where participants are in quarantine or unable to meet in person.

Challenges with FDA-Regulated Studies

The FDA's flexibility did not extend to all aspects of the consent process. Regulations under 21 CFR Part 11 for electronic signatures were still required, posing a challenge for rapid implementation. Some CTSA sites did have Part 11-compliant electronic signature systems in place, allowing them to continue using paper-based consent through telehealth platforms.

Alternative Consent Methods

For sites without a compliant eConsent platform, some creative solutions were used. Consent documents were often sent to participants before remote visits via digital platforms like DocuSign and PTrax, which enabled participants to review and sign documents electronically. For participants receiving consent forms via email, which does not support digital signatures, they would print and sign the form, then send a photo of the signed document back to the study team. [4]The study team would then print, sign, and upload the completed form into the electronic health record (EHR). This process ensured that consent was documented even if a fully electronic signature system was unavailable.

Adjusting Study Coordination During COVID-19

When states implemented stay-at-home orders due to COVID-19, research teams and sponsors had to decide which safety and primary outcome assessments were essential and which could be delayed or adjusted. This required reviewing each study's requirements and adapting them in line with FDA regulations, which allowed exceptions to protect participants from immediate risks. Research teams quickly collaborated with sponsors to develop study-specific plans that prioritized participant safety without compromising the study's integrity.

Switching to Virtual Assessments

To keep studies moving forward, many teams implemented virtual visits using phone calls or telemedicine. Telemedicine platforms allowed researchers to maintain regular contact with participants, conduct assessments, and ensure participants' safety from a distance. Participants generally responded positively to virtual study visits, appreciating the convenience and reduced exposure to COVID-19 risks. Virtual visits provided a safe and accessible alternative, making it easier for participants to stay involved in research without having to leave their homes.[5]

Use of Digital Tools and Self-Reporting

Before the pandemic, some research teams were already familiar with conducting remote assessments through survey tools like REDCap, Qualtrics, and Survey Monkey. Many studies had already begun using digital methods for participant self-reporting, such as electronic patient-reported outcomes (ePROs), electronic diaries (eDiaries), and tools like HUGO for data collection. These tools allowed participants to report symptoms, complete surveys, and record their health status from home, reducing the need for in-person contact.

Wearable Devices for Data Collection

Some CTSA hubs were also using wearable devices to track participants' health data, including vital signs, activity levels, sleep patterns, and even fall detection. These devices enabled researchers to collect continuous data remotely, giving valuable insights into participants' health without requiring physical visits. Wearable technology proved especially useful during the pandemic, allowing researchers to monitor participants' health in real time while minimizing COVID-19 exposure risks.

Challenges of Implementing Digital Tools and Wearable Devices

During the peak of the COVID-19 pandemic, introducing electronic data capture methods or wearable devices into clinical trials posed several challenges. Since these digital tools were not initially included in many study designs, adjustments were necessary to incorporate them. Additionally, though personal health technologies are widely used in everyday life, they had not yet become standard in clinical research, partly because many of these devices still required validation for scientific accuracy. Other issues arose when participants had limited familiarity with or access to digital tools, making it difficult for them to complete remote assessments. To address this, some research teams opted to gather data through telehealth sessions and manually input the results into case report forms (CRFs). Alternatively, surveys via REDCap and Qualtrics were sent by email, allowing participants to fill out assessments remotely.

Local Provider Support for In-Person Measurements

For studies where virtual assessments were insufficient, local healthcare providers assisted in gathering essential biometric data, such as vital signs, weight, blood pressure, and respiratory rate. To involve local providers, study teams first obtained approval from sponsors and Institutional Review Boards (IRBs). Additionally, before data from these providers could be shared, participants needed to grant permission. In cases where a complete set of vital signs could not be obtained, some study sponsors permitted a basic remote assessment with documented deviations, as long as it ensured participant safety. Despite this support from local providers, the primary investigator remained responsible for managing participant safety, data quality, and reporting any adverse events or lab findings.

Enhanced Data Sharing via Electronic Health Records (EHRs)

The use of EHRs greatly facilitated data sharing between research teams, local providers, and participants. For example, platforms like Epic Care Everywhere allowed data to be uploaded directly, while participants could also access and share their own records with the study team. This improved communication and helped maintain data accuracy across different sites and providers.

Future of Virtual Methods in Clinical Research

Although virtual methods posed some challenges, they are likely to become a permanent feature in clinical research. Remote assessments and digital data collection using wearable devices, smartphones, and sensors may become central to a decentralized model of clinical trials. These technologies offer the potential for continuous monitoring and early detection of adverse events, providing real-time insights between study visits. However, before digital methods are widely adopted, issues around data validation, device compatibility, privacy, and security need to be addressed. Collaborations with regulators will be essential to ensure that participants' rights are protected as digital tools become more common in research. The pandemic has accelerated the acceptance of these tools, paving the way for their broader use in clinical trials.

Laboratory Sample Collection and Management

Coordinating lab testing during the pandemic required flexibility and close collaboration with study sponsors. In cases where participants could not travel to the research

site, local home health agencies were engaged to collect blood, urine, or stool samples from participants at home, which were then sent to the research site for processing. Some sponsors also allowed lab kits to be shipped directly to participants, who could take them to nearby laboratories. Depending on the arrangements, samples were either processed at a central lab or analyzed locally. With participant consent, test results were shared with the main study site, where staff ensured that lab findings met trial requirements and recorded them in the CRFs. For participants whose conditions were stable, some studies allowed reduced lab testing, which was helpful in cases where virtual sample collection wasn't possible. This flexibility was essential, especially as nearly half of the programs reported a lack of virtual lab options. Imaging tests, such as X-rays or MRIs, could also be done locally, provided the study team could review the results remotely. These adaptations allowed research teams to continue vital safety monitoring despite the pandemic's challenges.

Drug Management Strategies

Managing study medications became a significant challenge for many CTSA sites during the pandemic, as they lacked virtual solutions to ensure participants received their medications safely and effectively. To address this, various methods were employed. For example, research staff personally delivered medications to participants, while others utilized medical delivery services like MedSpeed. Some sites offered curbside or valet pickup options for participants to collect their medications without entering the facility. In other cases, medications were shipped directly to participants' homes, and home health services were used for administering injectable medications. All these alternative delivery methods required prior approval from the Institutional Review Board (IRB).

Investigators and study sponsors had to carefully consider how these changes could affect participants. In particular, some participants might be more focused on managing their ongoing health conditions than on the risks associated with COVID-19. Therefore, study sites made it a priority to communicate any changes in the trial process to participants, explaining how these changes might impact their involvement and emphasizing the need for close follow-up during the study.

Compensation for Participants

Generally, compensation for study visits remained consistent, whether the visits were conducted virtually or in person. Many sites that typically provided checks or retailer gift cards for participant remuneration adapted by mailing these payments during the pandemic. Some CTSA hubs utilized Greenphire's ClinCard, a secure online payment system that allows for easy tracking and quick payments after each visit. As sites shifted to virtual visits, they began to gather necessary information, like W9 forms, using secure online tools such as REDCap instead of paper forms. Any changes in how participants were compensated due to the pandemic required modifications to the informed consent documents and approval from the IRB before implementation.

Transitioning to Electronic Documentation

Despite guidance from the FDA encouraging the use of electronic documentation, many clinical research teams were still relying heavily on paper records prior to the pandemic. However, the need to manage studies remotely led to a rapid shift towards electronic data capture and storage. Research teams needed to assess secure and HIPAA-compliant methods for collecting, storing, managing, de-identifying, and reviewing source documentation that met the requirements of their local institutions and sponsors. For studies regulated by the FDA, it was crucial to find solutions that allowed study monitors to access documentation for verification and to use sponsor-approved methods for obtaining electronic signatures.

To facilitate this transition, many sites employed existing technology systems that had already been approved by their institutions. They collaborated with sponsors to identify editable electronic documents—like fillable PDFs or Word files—that could be used for assessments and other source data. These documents needed to be stored within secure systems that complied with HIPAA regulations, such as Box, Microsoft OneDrive, SharePoint, and FileLocker. Using electronic health records (EHRs) helped streamline the process, as study sites could document research-specific procedures and assessments directly within the EHR. This included maintaining logs for adverse events and managing informed consent electronically. By entering data directly into electronic case report forms (eCRFs), study teams could ensure that all documentation was up to date and easily accessible, facilitating smoother study operations even during the challenges posed by the pandemic.

Transition to Electronic Documentation

The urgent need to switch to electronic documentation during the pandemic led many research sites to implement temporary solutions. However, as the field of clinical research evolves toward a decentralized model, it has become evident that electronic source data will require further exploration and development. The pandemic presented a unique opportunity to modernize some outdated research processes, allowing for electronic documentation to become a more effective and efficient way to capture and monitor clinical trial data in real time.

Study Monitoring Adaptations

The shift to remote monitoring for clinical trials was particularly smooth for sites using Epic as their electronic health record (EHR) system, thanks to its EpicCare Link feature, which complies with 21 CFR Part 11 regulations. When a remote monitoring visit was

requested, it aligned with the study's timeline and adhered to confidentiality and contractual agreements outlined in the study protocol. Once the necessary privileges were granted, study monitors could securely access participant records remotely through EpicCare Link.

Similar to in-person monitoring, site staff needed to be available to respond to inquiries and provide any required documents, especially those that were not stored in the EHR. These documents were shared using secure file-sharing services like Simple Share. Additionally, virtual video meetings were used for site initiation and qualification visits. Many sponsors reported that remote monitoring visits were successful and led to increased efficiency, and they expressed plans to continue using these remote processes even after the pandemic.

Regulatory Challenges and Compliance Audits

Some sites in the CTSA survey reported that institutional policies or regulatory issues posed obstacles to adopting virtual methods. There are significant regulatory concerns associated with virtual visits, including the development of informed consent processes for data collection, transmission, and sharing. Issues also arise around validating endpoints for claims, EHR data, and data obtained from digital health technologies. Furthermore, there are concerns regarding the security, privacy, and ethical implications of the chosen digital platforms.[5], [7]

The implementation of virtual technologies can be especially complex for multisite clinical trials because telehealth regulations vary by state. To assist with the transition of ongoing clinical trials to virtual platforms, both the FDA and the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) have issued guidance that offers some regulatory flexibility during the COVID-19 crisis. However, because virtual visits are a relatively new concept, institutions have been slow to adopt these changes.

Sponsors are often cautious about embracing unfamiliar processes, particularly given the costs associated with conducting clinical trials. Greater acceptance of virtual technologies will depend on the implementation of stronger security measures for remote monitoring to safeguard against data breaches during data collection, transmission, and storage. This includes addressing confidentiality risks related to participants' GPS or location data, which could be subject to legal actions and potentially lead to economic loss or stigma.

It is unlikely that the current leniency regarding HIPAA enforcement related to the use of noncompliant videoconferencing platforms in healthcare will extend beyond the public health emergency. This situation underscores the importance of addressing regulatory and compliance challenges as the field moves forward with virtual approaches in clinical research.

Lessons Learned from the Pandemic

The CTSA survey revealed that COVID-19 significantly disrupted traditional clinical research practices. It acted as a driving force that accelerated the adoption of technology-driven solutions, setting new standards for the field, organizations, and research teams. Many programs reported that they adapted their clinical platforms or introduced new virtual methods to support research activities, and they plan to continue these practices even after the pandemic.

The responses from the survey highlighted that successfully transitioning to virtual options necessitated strong coordination and collaboration among a wide range of stakeholders. This need for collaboration has also been recognized in official statements by experts in fields like cardiovascular disease and oncology. The rapid adoption of virtual and remote methods during the pandemic was made possible by innovation and enhanced communication among study teams, sponsors, research participants, health systems, informatics professionals, regulatory officers, and policymakers. Maintaining these relationships will be crucial after the pandemic to ensure the continued development and success of technological solutions in clinical research.

However, some CTSA hubs faced challenges in obtaining laboratory and physiological data and delivering investigational products to participants. In some instances, while virtual solutions existed, they were not accessible to study teams because their institutions had not implemented eSignature platforms that complied with 21 CFR Part 11 regulations for source documentation and informed consent.

Based on the collective experiences of the CTSA consortium, four best practices have emerged for academic health centers to facilitate a successful transition to virtual clinical research. These include:

1. **Conducting a Readiness Evaluation**: Assess the current capabilities and resources available to support virtual research activities.
2. **Fostering Coordination and Collaboration**: Engage a diverse group of stakeholders to ensure a unified approach in implementing virtual solutions.
3. **Incorporating Technology in Planning**: Consider technological factors during the trial design and planning phases to ensure that they are integrated seamlessly.
4. **Making Virtual Resources Accessible**: Ensure that study teams can easily find and utilize virtual tools and resources to support their research efforts.[6]

CONCLUSION

The COVID-19 pandemic served as a catalyst for utilizing remote capabilities in clinical research. By embracing remote research methods, we could potentially lessen the travel burden on participants. This shift could also make it easier for individuals in rural or underserved communities, as well as people with

disabilities, to enroll in clinical trials. Ultimately, this could enhance the generalizability of trial results, improve efficiency, and reduce costs. Access for participants, a key barrier identified by many CTSA programs, needs careful consideration. It is important to ensure that we do not worsen the existing digital divide, which can prevent some individuals from participating in research. A potential "silver lining" of the pandemic could be an improved ability to engage with and recruit diverse participants, as well as the capacity to deliver therapies and gather data remotely. The most effective approach may be a hybrid model that combines remote activities with in-person encounters as needed. Although clinical research will likely always require some face-to-face interactions, the pandemic has underscored the importance of flexibility and innovation in research methods.

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