Advanced Clinical

INSIGHT BRIEF

Virtualizing Clinical Trials in a Pandemic: Lessons Learned and Future Impacts on Drug Development

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Introduction

The impact of COVID-19 on clinical trials was swift and substantial. Travel bans and site closures forced a rapid shift in the running of physical clinical investigative sites toward purely virtual environments. While the concept of virtual clinical trials has been around for a number of years, the decision to run this type of trial was previously a matter of preference.

Since the pandemic began, sponsors have been implementing fully virtualized and hybrid trials out of necessity. These are bringing benefits including the potential to remain efficient and profitable by adapting quickly to these unforeseen circumstances. This Insight Brief, authored by experts from Advanced Clinical, examines learnings from the pandemic, including case studies of the successful use of virtual approaches to run more agile and adaptive trials. The authors explore how these advances may shape the future of drug development.

Responding to COVID-19

Several regulatory agencies have issued guidance on clinical trials during the COVID-19 pandemic with most documents encouraging the use of virtual elements (Sidebar 1).

Sidebar 1: Regulatory Guidance

FDA on the Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic:

"Sponsors should evaluate whether alternative methods for safety assessments (e.g., phone contact, virtual visit, alternative location for assessment, including local labs or imaging centers) could be implemented…to assure the safety of trial participants."

European Medicines Agency (EMA) on the Management of Clinical Trials during the COVID-19 (coronavirus) Pandemic:

According to current EMA COVID guidance, remote monitoring is possible. Off-site monitoring activities could include use of phone calls, video visits, e-mails or other online tools: "Certain sponsor oversight responsibilities, such as monitoring and quality assurance activities need to be re-assessed and temporarily, alternative proportionate mechanisms of oversight may be required. The first priority when considering any change is to protect the rights, safety and well-being of trial participants."

UK Medicines and Healthcare products Regulatory Agency (MHRA) Guidance on Managing Clinical Trials during Coronavirus (COVID-19):

"We support remote monitoring where appropriate…The MHRA will be as flexible and pragmatic as possible with regard to regulatory requirements for clinical trials during this time."

Enabling Transition to Virtual Trials: A Management Plan

Advanced Clinical adapted to the pandemic by transitioning to a more virtual environment using a five-pronged planning approach:

1. Development of internal procedures to support the continuation of trials, taking into account the need for:
   - Planned non-compliance
   - Risk mitigation plans, working closely with clients to minimize risks
   - A remote monitoring standard operating procedure (SOP), which was developed within several weeks
   - Site surveys to continue gathering relevant information
   - A COVID-19 Impact Form (DM)

2. Extensive communication with clients, based on:
   - An Advanced Clinical position statement clarifying plans for continuing trials
   - Review of the Advanced Clinical COVID-19 plan by project managers and teams
   - Executive-level calls with clients

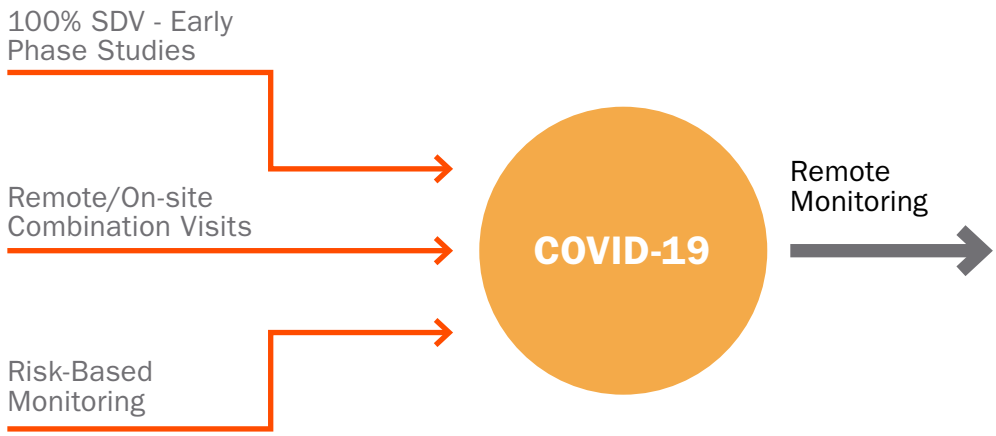
3. Clear internal communications with staff to raise awareness of new expectations, including:
   - Work-from-home communications
   - Daily COVID-19 meetings
   - Travel restrictions for clinical research associates (CRAs)

4. Close compliance with the latest regulatory guidance, including:
   - FDA, EMA and MHRA guidance
   - Participating in educational webinars and developing whitepapers

5. Formulation of an “exit strategy” to recover from the crisis mode and move into a “new normal”:
   - Committee established
   - Proactive planning underway

While the concept of virtual clinical trials has existed for several years, many sites were unfamiliar with implementation until this year. Thanks to COVID-19, sites and sponsors had to rapidly overcome a steep learning curve, adopting telemedicine, remote monitoring, and other virtual elements in real time. Remote monitoring in particular offers an adaptive and flexible environment, allowing monitors to dedicate more of their time to data review and risk mitigation, and less time to traveling and compiling manual documents (Figure 1).

Figure 1: Changes in the Concept Of Monitoring



Companies and sites that adapted rapidly were often able to maintain efficiency and profitability despite the crisis. However, despite the benefits, many smaller and mid-sized pharma companies were slower to adopt remote monitoring, in part because it requires significant investment in technology, training and changes to Standard Operating Procedures (SOPs). These companies may ultimately make this shift—even if rather unwillingly—due to the COVID-19 pandemic.

Four main scenarios were seen as companies and sites adopted remote monitoring, depending on their existing level of adoption and extent of digital data collection:

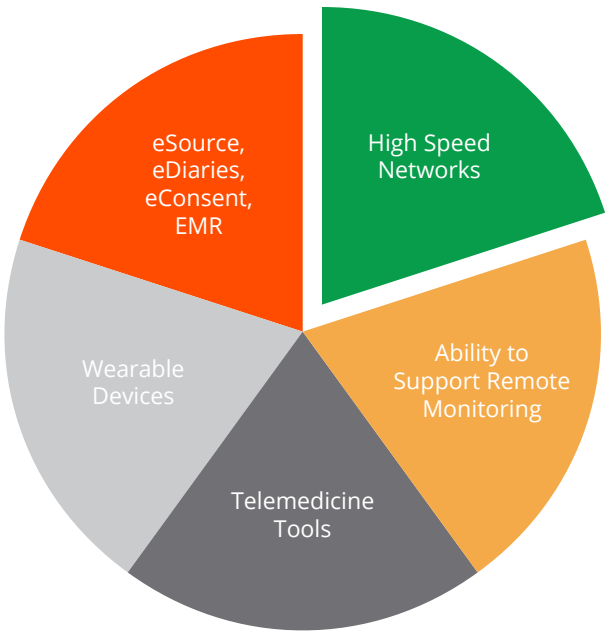
1. Rapid adoption at sites based in countries that allow remote monitoring and already had the technology and SOPs in place. In cases where sites were midway through a trial, transitioning to remote interim monitoring visits (IMV) could be achieved quickly if there was already a policy in place to allow EMR access to the electronic medical record (EMR). Use of electronic regulatory and pharmacy software solutions also enabled full virtual regulatory and investigational product (IP) accountability.
2. Innovative approaches to adapt at sites in countries that do not allow remote monitoring and/or lack electronic regulatory solutions and EMR access. The Advanced Clinical team works to minimize delays to data review and accelerate adaptation by working with institutions to establish an SOP for direct EMR access, and establish a remote IMV workflow so that remote monitoring can begin.
3. More elaborate solutions were needed at sites that are predominantly paper-based, including significant scanning of documents, implementation of new data platforms, and changes to existing SOPs. When working with these sites, Advanced Clinical customizes its approach to maintain monitoring momentum for the duration of the pandemic.
4. A tailored site approach for sites that choose to limit their EMR access due to institutional policies or EMR capabilities. Here, Advanced Clinical offers a hybrid approach using our secure solution for uploading documents ahead of a scheduled IMV. This gives the site time to prepare and redact agreed-upon sources based on critical data points affecting subject safety, eligibility and protocol endpoints.

Continued efforts are needed to make clinical trial participants comfortable in a remote environment, including offering home visits by nurses and phlebotomists, and use of local healthcare services, drug delivery services (...), and concierge services (...).

Moving Forward in the "New Normal"

To be successful in the "new normal," virtual approaches will continue to be essential, including technology platforms that can support eSource, eDiaries, eConsent and EMR; high-speed networks and connectivity to support technology solutions; telemedicine tools; and wearable devices for remote monitoring with minimal or no on-site visits (Figure 2).

Figure 2: Virtual Trial Technology: Enabling Change in Clinical Research



Continued efforts are needed to make clinical trial participants comfortable in a remote environment, including offering home visits by nurses and phlebotomists, and use of local healthcare services, drug delivery services (to provide investigational product), and concierge services (to help handle travel logistics when patient site visits are essential).

Elements of Success: Leadership Support, Willingness to Change and Adaptability

At the site level, four elements were key to enabling a rapid adoption of virtual elements:

1. Leadership buy-in was vital to the adoption of new technologies and remote monitoring.
2. Staff training (site and internal) eased discomfort and reduced the risk of errors.
3. Patient support solutions, including training and virtual concierges, helped patients embrace the "new normal" of virtual healthcare visits.
4. Sites that were open to making rapid changes were better able to maintain trial continuity and avoid a backlog of monitoring tasks.

Impacts of the EU General Data Protection Regulation

In many cases, local data privacy regulations complicate the transition to virtual trial technology, including the European Union General Data Protection Regulation (GDPR) (Sidebar 2).

Sidebar 2: The EU General Data Protection Regulation

- On May 25, 2018, the EU adopted the General Data Protection Regulation (GDPR) to protect citizens' personal data.
- GDPR allows for two encryption methods to secure personal data: standard encryption (unintelligible to those not authorized to access it even in case of data breaches); and pseudonymization (which encodes personal data with artificial identifiers such as a random alias or code).
- Pseudonymization is considered to be partial encryption, whereas encryption is viewed as the safest and most straightforward technique to secure data. Seamless encryption ensures the security of data during transfer as well as the security of static data.

In the case study described in Sidebar 3, innovative workarounds were used for data verification in a situation in the UK where GDPR rules did not allow remote monitoring.

A second case study is described in Sidebar 4, where stakeholder support was essential in enabling a remote site initiation visit.

Sidebar 4: North American Case Study - Phase 1 Oncology Stakeholder Support Ensures Successful Remote Site Initiation Visit

Situation:
In early April 2020, Advanced Clinical conducted a remote site initiation visit (SIV) with a large U.S. academic healthcare center. This was the first SIV for the phase 1 oncology study. The site involved did not typically allow remote SIVs but was eager to move forward to avoid delays in the program.

Solution:
Both the sponsor and site leaders were in attendance. The study coordinator provided a virtual tour of the facility via GoToMeeting. SIV attendees were able to see the pharmacy, discuss data collection methods and ensure that all trial data could be captured and shared. The entire remote visit was completed in just a few hours.

Results:
A highly productive, effective and efficient SIV was conducted. Following the virtual visit, the site team coordinated with clinic nurses, investigators and the pharmacy to remotely complete any remaining training. The entire experience went very smoothly, and everyone was highly satisfied with the results.

Sidebar 3: UK Case Study - GDPR Rules Prevented Remote Monitoring, Requiring Innovative Workarounds

Situation:
A small, UK site uses paperwork and electronic source options to monitor patients. During the pandemic, CRAs were unable to access the site. Due to GDPR, sites could not upload unredacted patient files.

Solution:
To meet monitoring requirements, the site coordinator read the data virtually to the CRA. When inconsistencies in data occurred, the verification stopped, and issues were addressed. Pharmacy contact occurred via intermittent calls for updates. The PI found this challenging because they were working from home.

Results:
Data verification took longer but was eventually completed over more visits. Advanced Clinical is currently exploring other avenues to have the sign-offs completed more efficiently within timelines.

Conclusion

Embracing lessons learned during the pandemic

On balance, Advanced Clinical's experience of adapting to the pandemic has been a positive one, with stakeholders—individuals, institutions, ethics committees (ECs), institutional review boards (IRBs), and competent authorities—going out of their way to be helpful, support the maintenance of clinical research and ensure patient safety. We have seen significant successes in the rapid development and implementation of COVID-19 Risk Mitigation Plans, which were highly appreciated by sponsors. Study awareness was increased through sponsor-CRO-site communications. Sites have been receptive to a collaborative approach to advance trials in challenging times.

Overall, training, culture change and stakeholder support are the keys to success. Virtual trial elements deliver many time, cost, quality and diversity benefits for sites and sponsors, including easing time and travel burdens for patients, reducing CRA travel burden, expanding patient populations available for trials, enabling investigators to oversee more patients in less time, and improved data quality.

More challenging situations arose based on certain local conditions, where the clinical trial staff were seconded to Emergency Room tasks, the IRB/EC were not able to meet (even remotely), and the focus of the Competent Authorities was on other COVID-related tasks. In addition, some sponsors were less receptive to change than others; some sites were not willing to participate in remote monitoring activities; there were challenges with site communication due to volume from various CROs/clients; there was an overall increase in protocol deviations directly attributable to missed in-patient subject visits; and country-level regulations impacted plans.

Overall, training, culture change and stakeholder support are the keys to success.

Key learnings from Advanced Clinical's experience during the pandemic includes the need to:

1. Build risk mitigation plans into every trial plan including those with virtual elements.
2. Ensure that all stakeholders are consulted, give approval, and that this is documented.
3. Consider using a hybrid approach using only those virtual elements that bring value to sites and patients and retaining other traditional approaches. It is not necessary to use a 100% virtual approach to benefit from these models.
4. Monitor regulatory opinions of virtual trials to ensure continuing compliance.

Sponsors should consider selecting a CRO partner that has hands-on experience running virtual trials; the ability to provide a roadmap for adopting these virtual approaches; flexibility to adapt SOPs quickly, reducing the likelihood of delays and other issues; and a proven risk management strategy to mitigate any future crises. Clinical development will continue despite any future challenges, and depends on an ongoing focus on patient safety, study data transmission rules, regulatory guidance and ensure detailed documentation and communication.

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A graduate of Warwick University, UK, Graham Belgrave has over 36 years of experience in successfully leading pharmaceutical development across clinical operations (phases I-IV), outsourcing and contract management, and project, program and vendor management. After starting his career in clinical operations, Mr. Belgrave moved to senior management roles overseeing clinical operations and later outsourcing and vendor management functions for global top pharma and biotech companies. Most recently, he served as COO at a specialty mid-sized CRO headquartered in the UK. Mr. Belgrave is an active member and Honorary Fellow of the Institute of Clinical Research UK (ICR), a Fellow of the Royal Society of Medicine, a Fellow of the Chartered Management Institute, a Chartered Scientist and a Member of the Institute of Biomedical Science, and an assessor for the UK Science Council.

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Domantas is a highly experienced, knowledgeable, and driven clinical monitoring professional responsible for leading and managing the North American Clinical Monitoring functional area at Advanced Clinical. He has extensive experience in various clinical monitoring roles and is currently the Sr. Director of Clinical Monitoring. Domantas' 12+ years of clinical research industry experience includes direct hands-on familiarity in managing phase I-IV studies in multiple indications including oncology, burns, urology, rare disease, endocrinology, CNS, and others. Domantas is knowledgeable in all aspects of clinical operations including operational and resourcing strategy development, proposal and budget management, and overseeing functional execution through process automation. Domantas is a graduate of Xavier University in Cincinnati, Ohio, and holds a Master of Health Services Administration as well as a B.S. in Arts and Sciences with an Entrepreneurship minor degree.

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