Decentralised Clinical Trials in Europe: *Lessons from a Pandemic*

Introduction
Many elements of decentralised clinical trials (DCTs) have long been available – including mobile devices, remote monitoring, telemedicine, and home health providers – but the decision to run these types of trials was simply a matter of preference. Since the onset of the COVID-19 pandemic, travel bans and site closures have forced a rapid transition from physical clinical investigative sites to virtual environments. DCTs have been implemented out of sheer necessity and have been critical to advancing clinical research by minimising in-person interactions. Benefits include the potential to improve recruitment, facilitate data collection, and reduce the need for travel by patients and CRAs alike, resulting in efficiencies and continued profitability. DCTs demand new roles and partnerships which will likely continue long after the pandemic comes under control.

This article focuses on learnings from the pandemic in Europe, including case studies of successful use of virtual approaches to run more agile and adaptive trials. The author explores how these advances may shape the future of drug development in this region.

Steep Learning Curve
After the emergence of COVID-19, sites and sponsors had to quickly overcome a steep learning curve to adopt telemedicine, remote monitoring, and other virtual elements in real time.

Sponsors and sites that adapted rapidly were often able to maintain efficiency and profitability despite the events created by the pandemic. However, many smaller and mid-sized pharma companies were slower to adopt remote monitoring, in part due to the need for significant investment in technology, training, and changes to standard operating procedures (SOPs). These companies are now increasingly making this shift, even if rather unwillingly.

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 travelling and compiling manual documents (Figure 1).

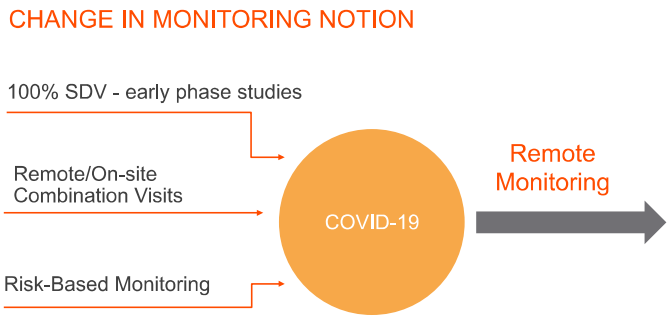

Figure 1: Changes in the concept of monitoring

Managing the Transition to DCTs
A five-part approach can be used by contract research organisations (CROs) to transition trials to a more virtual setting, comprising:

1. **Adaptation of internal procedures** to support the continuation of trials, taking into account the need for: planned non-compliance, risk mitigation plans, a remote monitoring standard operating procedure (SOP), site surveys to continue gathering relevant information, and development of a COVID-19 impact form for data management
2. **Close communication with sponsors**, based on a clear plan for continuing trials, review of this plan by project managers and teams, and executive-level calls with clients
3. **Internal communications** with the CRO's staff to clarify new expectations, including the need to work from home and comply with travel restrictions, which have been especially significant for clinical research associates (CRAs)
4. **Tracking and compliance** with COVID-related and other regulatory guidance, including attending educational initiatives such as webinars
5. **Devising an 'exit strategy'** to recover from emergency mode and move to a 'new normal', including setting up a working group and initiating proactive planning

On the regulatory front, guidance on clinical trials during the COVID-19 pandemic from the European Medicines Agency (EMA) and UK Medicines and Healthcare products Regulatory Agency (MHRA) broadly encourages the use of virtual elements *(Sidebar 1)*.

***Sidebar 1:* European regulatory guidance**

European Medicines Agency (EMA) on the Management of Clinical Trials during the COVID-19 (coronavirus) Pandemic
Under current EMA guidance, remote monitoring is possible during the pandemic. Off-site monitoring activities might include phone calls, video visits, and 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."[1]

UK Medicines and Healthcare products Regulatory Agency (MHRA) Guidance on Managing Clinical Trials during Coronavirus (COVID-19)
MHRA guidance states, "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."[2]

In many cases, local data privacy regulations have complicated 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**

The EU adopted the General Data Protection Regulation (GDPR)[3] to protect citizens' personal data on May 25, 2018. The GDPR allows for two encryption methods to secure personal data: ***standard encryption*** (unintelligible to those not authorised to access it, even in case of data breaches); and ***pseudonymisation*** (which encodes personal data with artificial identifiers such as a random alias or code).

Pseudonymisation is considered to be partial encryption, while 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.

Scenarios for DCT Adoption

As sponsors and sites adopted remote monitoring during the COVID-19 pandemic, four main scenarios have been seen, depending on the existing level of adoption and extent of digital data collection:

1. *Prompt adoption* at sites in countries where remote monitoring is allowed, and that already had technology and SOPs in place. For sites that were already mid-way through a trial, transitioning to remote interim monitoring visits (IMV) could be achieved rapidly if a policy was already in place to allow access to the electronic medical record (EMR). Use of electronic regulatory and pharmacy software solutions can also enable full virtual regulatory and investigational product accountability.

2. *Innovative approaches* were applied at sites in countries that do not allow remote monitoring, and/or that lack electronic regulatory solutions and EMR access. It is important to minimise delays to data review and accelerate adoption by establishing an SOP for direct EMR access, and to devise a remote IMV workflow, so that remote monitoring can begin.

3. Customised solutions were used at sites that are mainly paper-based, involving significant scanning of documents, implementation of new data platforms, and changes to SOPs. This approach aims to maintain monitoring momentum throughout the pandemic.

4. *Tailored approaches* were most appropriate for sites that choose to limit their EMR access due to institutional policies or EMR capabilities. Here a hybrid approach can be helpful, using a 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.

Technology Platforms as a Key to Future Success

To be successful as the 'new normal' evolves, virtual approaches will remain 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 onsite visits (Figure 2).

Continued efforts are needed to make clinical trial participants comfortable in a remote environment, including offering home

VIRTUAL TRIAL TECHNOLOGY: ENABLING CHANGE IN CLINICAL RESEARCH

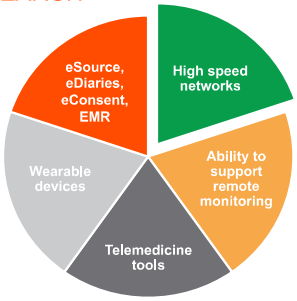

Figure 2: Types of virtual trial technology

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).

In this new environment, certain skill sets are becoming more prominent, with a need for a shift in mindset and use of differing strategies, and all involved stakeholders must be open to this. Strategic thinking and flexibility will continue to be vital, along with strong communication, adaptability to new and changing technology, and the ability to manage an increased volume and speed of data collection (Figure 3).

CHANGING SKILL SETS

Figure 3: Changing skill sets

UK Case Study: Innovative Workarounds

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.

***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

Experience during the pandemic has on balance shown that stakeholders – individuals, institutions, ethics committees (ECs), institutional review boards (IRBs), and competent authorities – have supported the continuation of clinical research while protecting patient safety. Rapid development and implementation of COVID-19 risk mitigation plans have played an important role. Study awareness was successfully increased through sponsor-CRO-site communications, and sites have been receptive to a collaborative approach to advance trials in challenging times.

Training, culture change, and stakeholder support have been repeatedly shown to be key 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 have occurred based on certain local conditions; for example, where the clinical trial staff were seconded to emergency room tasks, the IRB/EC were not able to meet (even remotely), and the competent authorities were focused on other COVID-related tasks. Other challenges have included some sponsors being less receptive to change than others; some sites being unwilling to use remote monitoring; issues with site communication; an overall increase in protocol deviations directly attributable to missed in-patient trial participant visits; and barriers due to country-level regulations.

Lessons learned during the pandemic include the need to:

1. Have risk mitigation plans within every trial plan – including those with virtual elements.
2. Consult all stakeholders, gain their approval, and document this step.
3. Consider using a hybrid approach with specific virtual elements that bring value to sites and patients, and retaining other traditional approaches. A 100% virtual approach is not required to benefit from these models.
4. Closely monitor regulatory opinions and guidance on virtual trials to ensure continued compliance.

Applying these learnings will help ensure that the benefits of DCTs can continue to be reaped in future.

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