

Decentralised clinical trial adoption: lessons learnt from the pandemic

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ABSTRACT

The COVID-19 pandemic highlighted the need for, and accelerated the adoption of, decentralised clinical trials (DCTs). Regulatory intelligence (RI) functions have played a key role in developing DCT strategies during the pandemic to enable some sponsors of clinical trials to maintain continuity during this period of extreme uncertainty. In this article, we look at lessons learnt from a contract research organisation (CRO) perspective, which may aid RI functions supporting the rapidly evolving area of flexible DCT models beyond the pandemic.

Introduction

The COVID-19 pandemic significantly impacted the clinical research model. Patients who had been participating in clinical trials could no longer access hospital trial sites to receive treatment and/or for follow-up visits due to government travel restrictions or because they did not wish to attend for fear of potential infection. As government restrictions took effect further, complications emerged at clinical trial sites worldwide, such as the inability of clinical research associates (CRAs) and site inspectors to access hospital trial sites for trial oversight purposes, delays in supply of investigational medicinal product (IMP), which in certain cases also had a knock-on impact to IMP stability, sites suspending research activities and regulatory authorities (RAs) and ethics committees (ECs) suspending activities or working at reduced capacity.

Rapid response was required to overcome the unprecedented pressures faced. Early in the pandemic, recognising the barriers impeding clinical research, RAs worldwide began releasing a myriad of regulatory guidance covering extensive topics such as interim clinical trial management, emergency measures to enable trial continuity, and innovative regulatory procedures. Regulatory intelligence (RI) functions came to the fore because of their ability to keep pace with the fast-changing regulatory requirements, interpret and identify trends, and feed intelligence to stakeholders to enable trials to adapt.

In the context of clinical trials, adaptation typically centred on the introduction of flexible trial models and digitally enabled solutions, including hybrid or full decentralised clinical trials (DCTs), that enabled early adopter companies to overcome challenges arising due to the pandemic. Figure 1 provides examples of typical headwinds faced by the clinical research industry during the pandemic, along with digitally enabled solutions that were permitted by many RAs, often with provisions, to overcome each challenge.

Decentralised clinical trial models

Several definitions of DCTs exist, penned by RAs and other organisations, including the US FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA),¹ the Clinical Trials Transformation Initiative (CTTI)² and the Association of Clinical Research Organizations (ACRO).³ The various definitions share key underlying principles, essentially summarising DCTs as trials involving patient participation away from sites, either partially (hybrid DCT) or entirely (full DCT), through the use of various

digitally enabled solutions such as televisits, direct-to-patient supply, and remote electronic patient consent (shown in Figure 1).

DCTs offer many potential benefits over traditional trial models, including reduced burden on patients and sites, greater patient access and patient diversity, expanded geographic reach, increased emphasis on patient engagement and patient-centricity, and time and cost savings. Even before the pandemic, RAs and the industry had taken steps toward embracing DCTs. For example, in 2017 the FDA set out a Digital Health Innovation Action Plan⁴ to strengthen expertise in its digital health unit. The CTTI released recommendations for DCTs in 2018 and again in 2019.⁵ In its 2018 manifesto⁶ the European Federation of Pharmaceutical Industries and Associations (EFPIA) proposed adopting new trial designs involving digital tools to support the EU becoming a world leader in clinical trials. In 2019, ACRO established a committee to study the benefits and challenges of DCTs,³ and the Innovative Medicines Initiative (IMI) launched the “Trials@Home project”, exploring use of digital technologies in clinical trials.⁷

Early in the pandemic, RAs generally advised that interim measures supporting continuity would be revoked once the health crisis subsided. However, subsequently, some RAs, including the FDA, advised that lessons learnt and precedents set during the pandemic for a range of activities and processes including DCTs may lead to permanent changes in the future.⁸ Furthering its commitment to embracing digital tools, in September 2020 the FDA launched a Digital Health Center of Excellence (DHCoE), an important milestone in the agency’s planned evolution of its digital health programme, helping to advance innovative digital health technology to benefit patients.⁹ In collaboration with the Heads of Medicines Agencies (HMA), in December 2020, the European Medicines Agency (EMA) released its Network Strategy to 2025, which lists data analytics, digital tools and digital transformation among its areas of strategic focus in the coming years.¹⁰ Industry reports show the DCT market is growing; according to a report by Polaris Market Research, it is expected to grow at a compound annual growth rate (CAGR) of 12.6% from 2020 to 2027.¹¹

Regulatory authority acceptance of digital solutions during the pandemic

Before the pandemic, uptake of DCTs was relatively slow despite efforts by various stakeholders, as previously noted. However, the pandemic necessitated the urgent need for flexibility in clinical trials, resulting in many RAs permitting the use of digitally enabled activities as interim measures

FIGURE 1

Headwinds faced by industry during the COVID-19 pandemic

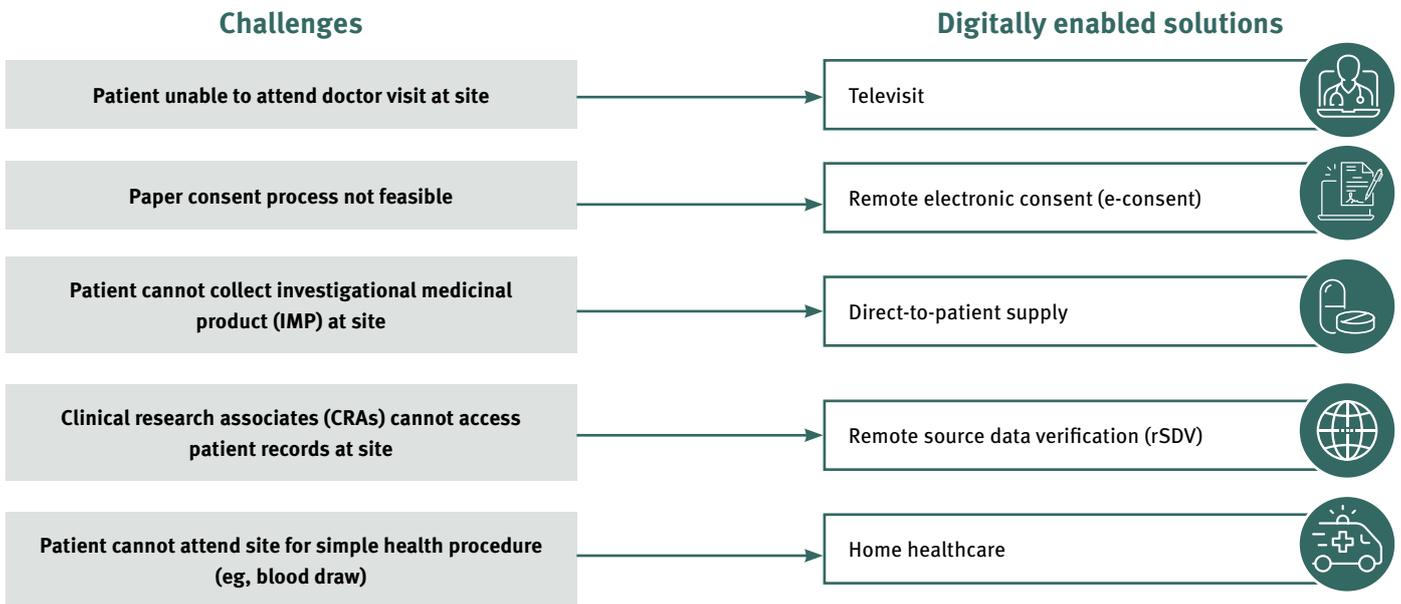
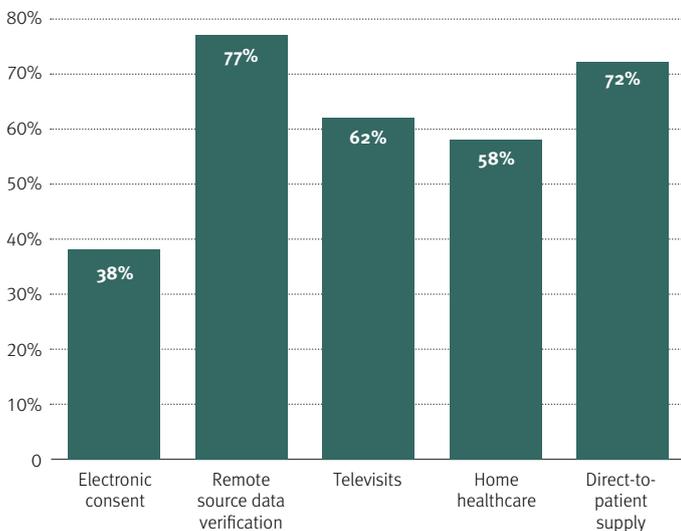


FIGURE 2

Acceptance of digital trial solutions across 74 countries



Source: PPD RegView (February 2021)

to support continuity and safeguard patient safety. Regularly, RI functions were responsible for gathering, interpreting and disseminating intelligence to operational teams to enable trials to adapt and inform strategy.

Maintaining RI for these and other digital solutions proved challenging for various reasons, including the high volume of new and updated RA guidance across countries/jurisdictions, lack of harmonisation across RAs, and information being published by different RAs at varying levels of granularity. Some RAs did not publish guidance on certain digitally enabled activities at all, requiring frequent communication to ascertain the intelligence.

Examples of DCT solutions that frequently were permitted or even recommended by RAs during the pandemic are listed in Figure 2, along with

levels of acceptance across 74 countries based on intelligence maintained in an in-house RI database (valid as of June 2021). Table 1 provides a brief description of each solution and sample RI gathered across multiple countries. Generally, intelligence varies at the jurisdiction, country and/or state level and is trial-specific, dependent on factors such as study phase and patient population. Full RA guidance for each location should be consulted before making any decisions relating to DCT strategy and all trial nuances considered in order to maximise DCT activities, de-risk utilisation of digital trial solutions and develop appropriate strategy.

Regulatory considerations for introducing digital solutions

RI functions have been able to identify common themes from guidance documents published by RAs across jurisdictions regarding key regulatory considerations for introducing digitally enabled solutions during the pandemic. It is expected many of these considerations will apply to DCTs after the pandemic subsides.

Examples of common themes and key regulatory considerations for DCT strategies are provided in Figure 3, and several important ones are discussed in more detail here:

- Risk-based approach** Decisions to incorporate digital aspects should be based on risk assessment by the sponsor, taking limitations and risks into account, and in conjunction with investigators where appropriate.
- Patient-centricity** Many clinical trials, IMPs and/or patients are not suitable for or adaptable to DCT. Therefore, a patient-centric approach is essential, while appropriate use of DCTs must be considered. Digitally enabled activities must safeguard patient safety, maintain compliance with good clinical practice (GCP) and minimise risks to trial integrity.
- Communication and consent** Communication with regulators is key. Early consultation is recommended when considering adapting ongoing trials to DCTs. Patients should be informed when introducing digital solutions, and informed consent obtained when appropriate.

TABLE 1

Examples of flexibilities granted by RAs during the pandemic and associated intelligence

Digitally enabled solution	Description	Flexibilities and associated regulatory intelligence (examples)
Remote e-consent	Informed consent form (ICF) taken by electronic means, and in scenario whereby the patient is not present at the clinical trial site.	Some RAs previously prohibiting remote e-consent permitted its use during the pandemic, and in some cases with provisions, eg, the use of postal transfer of signed copies; ICFs sent to patient for perusal at home with telephone call or video conference to discuss the content and clarify any questions; language of e-consent must confirm the methodology explicitly via “e-consent via video conference with ability to ask questions” or “remote e-consent with e-signature or biometric signature (eg, fingerprint)”; site files PDF in e-file for at least 25 years; the patient must receive a printed version and/or electronic locked copy of the signed and dated electronic ICF. Trial sites/patients always have the right to refuse e-consent process.
Direct-to-patient (DtP) supply	IMP supplies are shipped directly to the patient’s home from the site, distribution centre or depots.	Many countries permitted DtP supply during the pandemic on an exceptional basis only and/or with provisions, such as: supply from the site or depot only (ie, not direct supply by the sponsor); only for IMP that can be administered at home; consideration required concerning general storage in the home, maintaining stability during transit (especially cold chain product), safe custody and IMP accountability management.
Remote source data verification (rSDV)	A check that the data collected on a research study can be verified by looking at a primary source (eg, medical record). Remote SDV (rSDV) involves conducting this task away from the trial site using technology.	Before the pandemic, rSDV generally was prohibited by many RAs. As the pandemic continued more RAs permitted this activity but typically with strict provisions. For example, in some countries it has been permitted for trials assessing treatment/vaccine for COVID-19 only or for pivotal studies approaching database lock. Due to the nature of rSDV it is advisable that implementation be carried out in close collaboration with the site investigators. The investigators should consult relevant personnel at the hospital regarding possible solutions, practicality and security given the associated data privacy risks.
Televisits	A medical visit that takes place via computer or telephone instead of on-site.	Many RAs encouraged sponsors to utilise televisits during the pandemic when possible. In some countries, eg, France, approval by RA and EC, as well as the Data Privacy Authority may be required before implementation, which can take some time (eg, four-month approval timeline by French Data Privacy Authority) and therefore should be factored in to avoid study startup delays. Patient consent also required in some countries.
Home healthcare	Nurse/doctor visits the patient’s home in place of patient attending site.	Some RAs have permitted healthcare at home provided by physicians and/or certified nurses, often under principal investigator (PI) oversight and in some cases covered by sponsor/PI liability insurance. For some countries, in the case when a vendor provides the service, it must be contracted directly by the site, ie, a CRO/sponsor cannot contract the home healthcare vendor directly.

- Data protection and IT security considerations** A key privacy risk for use of certain digitally enabled solutions relates to the potential for unauthorised access and loss of named medical data. Robust security controls are essential to avoid this. Additionally, local requirements for data protection and IT security considerations may exist and should be considered.

Practical considerations for RI functions supporting DCTs

The pandemic presented industry and patients with extraordinary and unprecedented circumstances that have tested the limits of utility of digitally enabled solutions and regulatory allowances. On various occasions RAs around the world refined their guidance, in some cases to provide more information on such solutions. For example, in the third edition of the EMA guidance on the “Management of Clinical Trials during the COVID-19 Pandemic”, dated 28 April 2020, extensive information was added relating to remote source data verification, and further clarification was provided in the fourth version dated 4 February 2021.¹² The FDA also refined its guidance on multiple occasions (the current edition, dated 27 January 2021, is the ninth revision¹³) as more experience was gained and refinements became necessary.

Organisations and sponsors also gained valuable experience during the pandemic, which helped formulate trial continuity plans and shape

evolving DCT strategy. Figure 4 highlights some practical considerations, based on lessons learnt during the pandemic, that may benefit RI functions supporting DCTs. In terms of RI processes and gathering intel, particular attention may be required to ensure terminology relating to DCTs, which may be new to colleagues, is understood across groups responsible for screening in order to align and promote accuracy of intelligence, such as understanding the difference between “remote monitoring” and “remote source data verification”. Introduction of an organisational-wide DCT glossary of terms, RI digital subject matter expert (SME) and hosting RI workshops for associates gathering the intelligence may encourage cross-functional awareness and understanding. Given this is a rapidly evolving area, a multipronged approach to dissemination of intelligence may prove beneficial, such as use of an RI database/platform to enable all company associates’ access to global intelligence in real time, in addition to weekly RI updates, e-bulletins and monthly newsletters to communicate changes.

An expected upcoming challenge for RI functions will be anticipating and managing jurisdiction/country/state level intelligence and requirements as countries emerge from the pandemic, likely at different rates. Some RAs may allow continuation of activities that were permitted during the pandemic, while others may do so to a lesser extent or not at all. For example, in June 2021 two RAs (Czech Republic and Israel) announced rollback of some of the regulatory flexibilities that had been permitted during the pandemic.

FIGURE 3

Regulatory considerations for introducing digitally enabled trial solutions

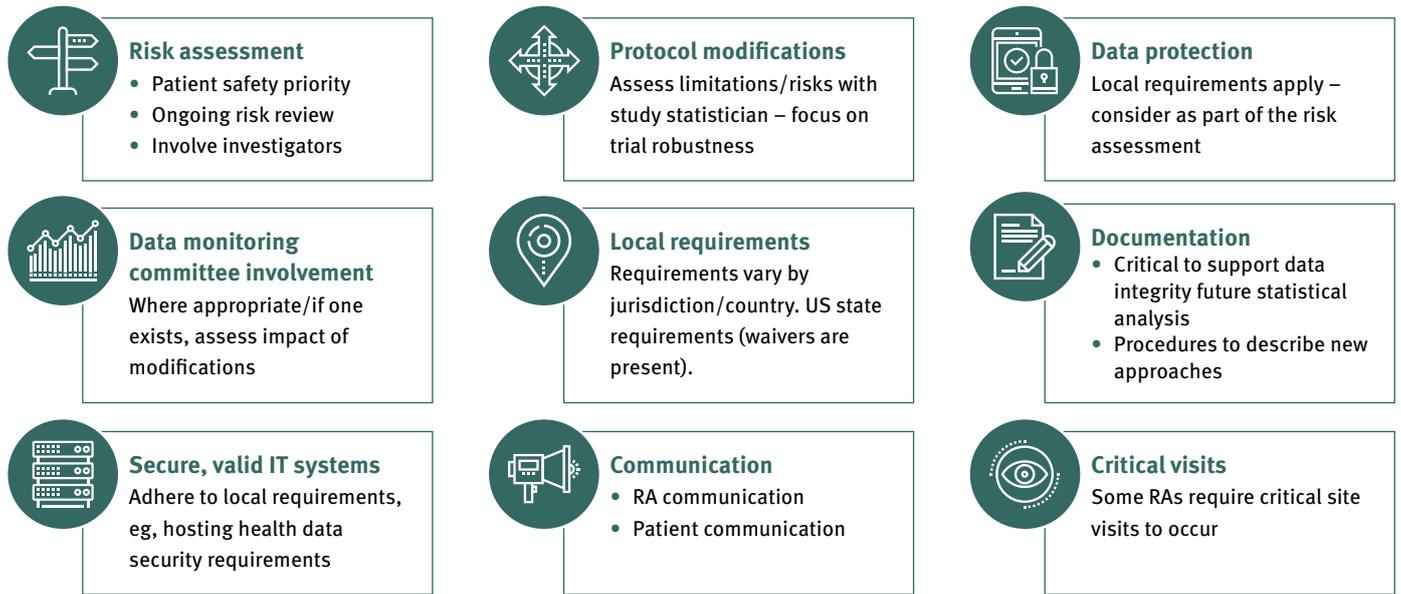
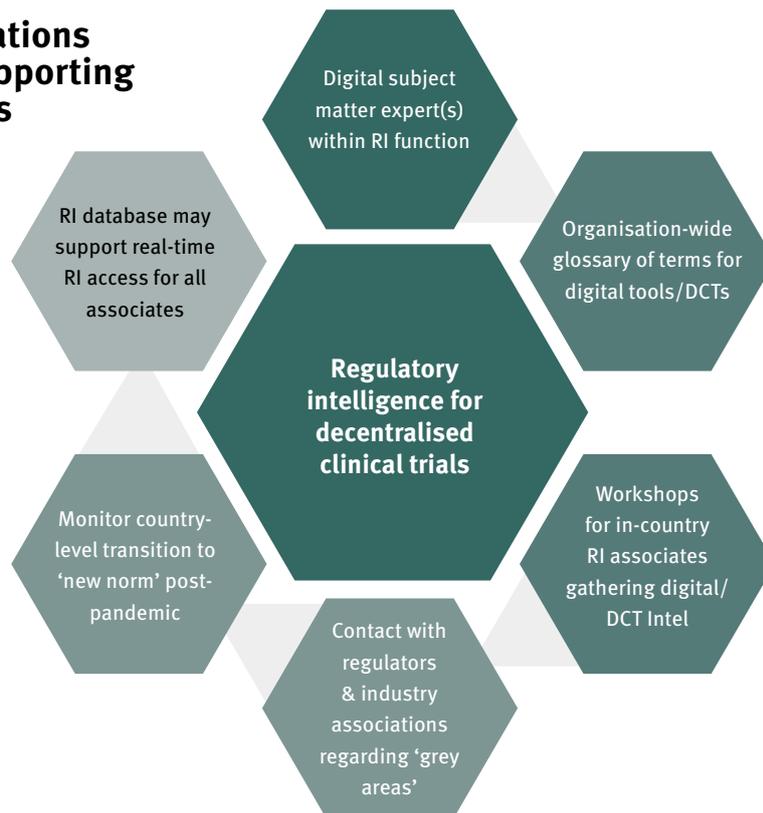


FIGURE 4

Practical considerations for RI functions supporting decentralised trials



Consideration of the items listed in Figure 4 may support effective RI screening and gathering for DCTs, particularly as the industry transitions out of the pandemic.

Conclusion

Flexible DCT models are being heavily relied on during the pandemic to maintain continuity to patients and to conduct trials seeking treatments and vaccines for COVID-19. Increasingly, pharmaceutical and biotechnology

companies are shifting to flexible, digitally enabled trial strategies, industry associations are advocating their use and regulators around the world appear open to exploring the possible benefits of digital tools in clinical research. Various RAs have indicated willingness to further adopt DCT strategies following the pandemic.

The RI function has played a central role in screening, gathering, maintaining, interpreting and disseminating vast arrays of intelligence relating to DCTs in a short time during the pandemic. Concepts and principles

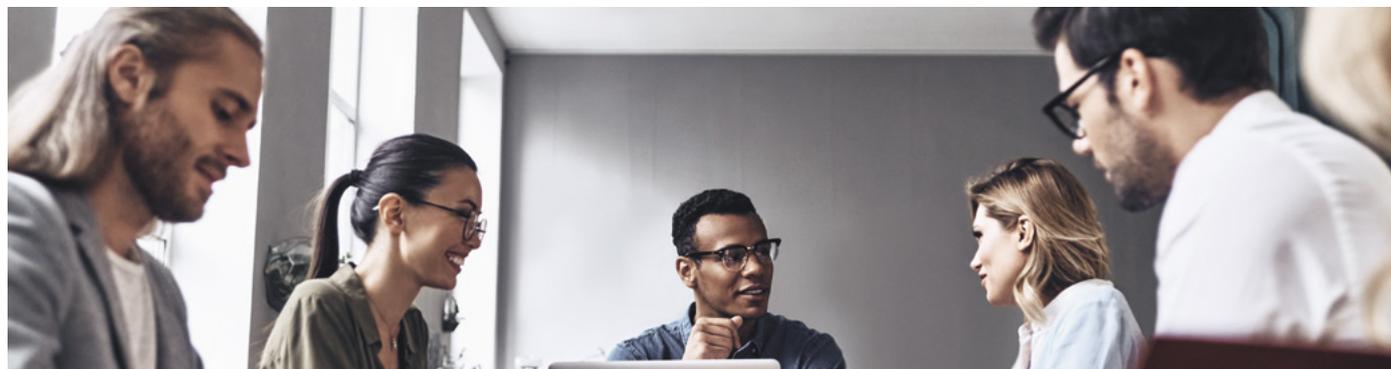
that were previously rarely applied have become widespread with the progressive adoption of digital solutions. One by-product of the pandemic has been the significant volume of experience gained for DCTs in a relatively short time. The RI function is well placed to maximise this experience to help inform future DCT strategies, particularly as the pandemic subsides.

The examples provided here only touch the surface, highlighting that a depth of RI is required to appropriately implement DCTs in such a manner that will safeguard patient safety, GCP and data integrity while complying with RA requirements. The experience of the pandemic has clearly demonstrated there is no one-size-fits-all model when it comes to DCTs. Factors such as trial suitability, patient acceptance, data privacy and IT security considerations, stakeholder buy-in, and operational readiness, as well as regulatory acceptance, are all necessary to implement successful DCT strategies.

As the regulations and industry evolve there is also a need for the RI function to innovate and adapt to the increasingly digital-focused era of clinical trials. As demonstrated by the experiences of the pandemic, RI functions are uniquely placed to support critical business strategy and can bring insight and awareness to enable companies to take advantage of the current momentum and move forward with perspicacity in the novel and exciting area of DCTs. ■

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