Decentralized trial tools and technologies are here to stay: A regulatory perspective

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Decentralized clinical trial (DCT) strategies and tools such as telehealth visits, centralized monitoring, and remote source data verification (SDV) gained traction overnight during the Coronavirus Disease (COVID-19) pandemic, while already common practices such as direct-to-patient (DTP) drug delivery and home nursing became even more widespread.

Regulators rapidly adjusted the rules on protocol deviations in unprecedented ways to ensure the continuation of clinical research. For example, when the World Health Organization (WHO) declared COVID-19 a global pandemic in March 2020, both the FDA and EMA issued guidance on conducting clinical trials (CTs) that allowed the substitution of remote approaches for on-site activities. In all, dozens of health authorities (HAs) around the world published pandemic rules.

As some countries slowly start to bring the pandemic under control, many companies are wondering whether clinical research will revert to the old ways? The short answer is no.

Prepare for a future of DCTs and hybrid trials

We can't put the DCT genie back into the bottle, because digitization, automation, and remote technologies allow for faster, patient-centric development of new therapies and amplify diversity in clinical trials.

These days, digital technologies are ubiquitous in daily life. Clinical trials won't revert to a paper-based, traditional approach because patients and site staff both expect the speed and convenience of device-based systems. Likewise, regulators would like to find ways to replicate the innovation, creativity, and extraordinary speed of COVID-19 vaccine development for other health challenges. Their aim is to make drug development more efficient while protecting patient safety and data integrity.

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Here are three ways to can manage risks while transitioning to more efficient decentralized and hybrid trials that incorporate more digital and remote tools:

1 Know the landscape for DCTs and remote tools.

Certain clinical trials cannot be fully decentralized because of issues such as the characteristics of the patient population, necessary medical surveillance, or digital device data privacy rules, but most clinical trials can incorporate decentralized elements. The key is to implement tools and processes that increase efficiency, reduce burdens on patients, and protect public health.

A lack of international harmonization around the transmission of patient data prevents trial sponsors from uniformly adopting remote technologies. For example, electronic informed consent (eConsent) saves time and allows patients with limited mobility to participate in clinical trials, but many countries have no regulations in place that would enable e-signatures and eConsent. Countries like the United States, the United Kingdom, Canada, Brazil, Italy, India, and South Korea allow eConsent, while China, Taiwan, Hong Kong, South Africa, and some Latin American countries do not. eConsent is also subject to approval from institutional review boards (IRBs) and institutional ethics committee (IECs) at the local level, so companies must know the rules for each study site.

In the EU, the General Data Protection Regulation (GDPR) limits the use of remote monitoring visits (RMVs) and SDV because they require transmitting patient data. Companies must guarantee adequate patient data privacy and security in many European countries, even when working with de-identified patient data. Spain has shown interest in adopting

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RMVs, SDV, and source data review (SDR), and Italy is working on legislation. The UK's Medicines and Healthcare products Regulatory Agency (MHRA) plans to update its guidance on remote monitoring of trials, including clarification of its short- and long-term expectations. With some of the tightest data security laws in the EU, France will need to amend national laws to align with any loosening of the GDPR.

EU guidance documents issued during the COVID-19 crisis showed exceptional flexibility regarding remote data access and most EU countries are likely to align with any new guidances going forward. In the United States and Canada, RMVs and SDV are possible, as long as companies can demonstrate they will access data through a validated system with layers of protection.

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The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is currently rewriting its Guidelines for Clinical Practice (ICH E6 GCP (E3)). Those new guidelines are expected to be published at the end of 2021, followed by a period of public consultation. In April 2021, the ICH released a draft GCP Principles document that proposed a risk-based approach to Guidelines for Clinical Practice that included innovative technologies while still protecting clinical trial participants. The impending release of new ICH guidelines could change the DCT landscape for companies conducting trials in ICH member countries.

2 Write flexible protocols.

Companies can embed flexibility into clinical trial protocols by including multiple options for patient visits, procedures, laboratory tests, drug delivery, and other activities. Ideally, it's best to build two scenarios for performing every task either remotely or on-site. That way, even if national legislation varies among participating countries, protocols will only need minimal amendments or revisions.

Investigators need the authority to make choices in implementing the protocol to fulfill their medical and regulatory responsibilities for patients' safety and well-being per ICH-GCP and other national and professional laws. This flexibility is most important when investigator tasks are delegated, such as during home nursing visits. Protocols should also give patients choices about whether they want to use remote DCT tools such as telehealth, wearables, e-Consent, or DTP delivery.

Telehealth visits and remote data collection and verification were relatively untested DCT innovations that saw sharp uptake during the COVID-19 crisis. At the peak of the pandemic, 57% of patient interactions were taking place remotely, according to a recent survey of 245 clinical trial investigators and study coordinators. A large majority (78%) of investigators believe telemedicine consultations will persist into the future.

Even a widely accepted DCT technique like telemedicine involves careful planning. For example, the informed consent form (ICF) must describe precisely how telemedicine consultations or any other video interactions with healthcare providers will work. Without a formal process in place,

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telemedicine can easily run into trouble with technical glitches and user error. A telemedicine "visit" through an app involves sending an invite to a patient, having the patient accept the invite, and making sure that everyone has a functional internet connection and is able to join the visit on the right day at the right time.

The Association of Clinical Research Organizations (ACRO) recently published a quality-by-design manual for DCTs that can help companies design flexible protocols.

3 Use remote solutions whenever you can justify it.

The pandemic forced sponsors to find ways to perform clinical research functions remotely and regulators to respond. Now, as Acting FDA Commissioner Janet Woodcock recently declared, remote clinical trials are "here to stay." In its COVID-19 Pandemic Recovery and Preparedness Plan (PREPP) Initiative report, the agency vowed to support "sustained innovations in clinical trial conduct" with new guidance.

In the EU, the Danish Medicines Agency has set the pace for adopting remote practices with its DCT guideline, issued in May 2021. The EMA will likely formalize a cohesive approach to DCTs across the EU within a few years.

Regulators still have the same top priorities: patient safety, good clinical practice compliance, and minimizing risks to data integrity. But they have officially acknowledged that DCTs and remote tools are inherently patient-centric. By allowing more patients to participate in trials in a shorter timeframe, DCTs can provide better evidence for physicians and regulators to make clinical decisions.

That said, companies should always focus on their patient population as they select and utilize new tools. For example, the Danish DCT guideline notes that increased use of digital media may deter "less tech-savvy" trial participants, possibly introducing selection bias. Similarly, some patient populations may find home nursing visits a deterrent for participation for personal, cultural, or economic reasons. Companies need to plan DCTs carefully to avoid unintended consequences.

Digitalization can also help companies work with agencies more efficiently while protecting public health. For example, companies routinely met with regulators via videoconferencing instead of phone calls or in-person visits during the pandemic. In the EU, face-to-face meetings and scientific advice sessions are now almost entirely remote. It's likely that trend will continue because it has worked well thus far.

Even in countries where the supporting legislation is still developing, companies can justify DCTs and virtual solutions by linking such practices to the worthy goals of reducing patient burdens in clinical trials and increasing efficiency in regulatory interactions.

COVID-19 led to an era of remarkable regulatory flexibility and innovation with DCTs. Moving forward, companies and patients alike can reap benefits by continuing to push the boundaries of conducting clinical research remotely.

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