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WHITE PAPER

Decentralized Clinical Trials: The Future of Clinical Research Is Here

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Introduction

Innovations in clinical trials are needed to significantly impact and improve key pain points in operational execution. Improvements in technologies and methods to drive clinical trial innovations have focused on the incorporation of decentralized clinical trials (DCTs)—also sometimes referred to as "remote," "hybrid," "virtual," or "patient-centric" trials (Medidata, 2020). The COVID-19 pandemic has significantly accelerated the adoption of DCTs, which allowed sponsors and CROs to quickly virtualize many trial activities, including remote monitoring, telehealth visits, electronic consent (eConsent), electronic patient reported outcomes (ePRO), electronic clinical outcome assessments (eCOA), and use of wearables/sensors. The uptake in DCTs is expected to continue in a post-COVID-19 world due to the experience gained during the pandemic.

The major benefits of DCTs include their potential to enhance the patient trial experience, deliver medicines to market faster, drive value demonstration, and offer greater time, and cost efficiencies. These improvements may finally provide a realistic solution for offsetting the ever-increasing costs associated with drug and device development (Apostolaros, 2019; DiMasi, 2016). However, to reap the full benefits offered by DCTs, it is imperative that the patient experience is optimized by ensuring that novel technologies deployed in a DCT offer convenience, reduce burden, and are easy to use.

Since DCTs are independent of geographic location and are implemented using digital health technologies and mobile/local healthcare providers, they have the potential to eliminate many of the constraints associated with traditional trial designs, including difficulties with recruitment and retention of sites and participants, and challenges in obtaining a wider variety and more frequent data points. By reducing the burden of participation, DCTs have the potential to increase the size of the patient pool for recruitment and shorten enrollment timelines. Improvements in data quantity and quality are more easily achieved, as measurements can be more frequent (e.g., sensors/wearables that take measurements 24 hours, 7 days a week), more robust (e.g., data collection can be integrated into a patient's real-life routine), and more comprehensive. Combining disparate data streams—such as real-world data in combination with clinical trial data—offers the opportunity to develop highly comprehensive patient profiles that are more informative with regards to how patients are affected by drugs and diseases.

It is expected that the use of DCT technologies within trials will increase, with estimations that 70% of trials will use one or more of these digital health technologies within the near future (Myshko, 2019). Further, by combining DCT capabilities—including eConsent, ePRO, eCOA, virtual visits, sensors/wearables, and patient registries—into a single unified platform, study teams can work off of a single data architecture that provides streamlined workflows, and can shorten time to study close and database lock by leveraging automated and intelligent tools that employ a risk-based approach to data management. Ultimately, unified and flexible DCT platforms can drive value demonstration of new therapies, which can increase patient access and differentiation in the marketplace.

This white paper provides an introduction to DCTs and summarizes the state of the industry from the perspective of different stakeholders, including the pharmaceutical and medical device industries, regulators across the world, and patients.

What Are Decentralized Clinical Trials?

DCTs, which can follow a range of approaches, are trials that consist of a blend of core features, such as having all visits conducted using telemedicine or using home visits, data are captured remotely using digital health technologies, direct-to-patient drug supply, and no physical sites employed (CTTI, 2018). As in traditional site-based trials, DCTs are led and coordinated by an investigative team and can be multisite with global reach. The major difference is that DCTs focus on bringing the trial directly to the patient; data collection is completed in the home or within the community, independent of geography.

The DCT model provides several benefits to patients and sponsors when compared to traditional trials. Patients enjoy convenience, less travel burden, and increased trial access, while sponsors may see accelerated recruitment (in an environment with increasing competition for patients), increased patient engagement and retention, a broader and more diverse patient population, time and cost savings, and seamless multisite management. Prior to embarking on a DCT, consideration should be given to who will support and manage the technologies that will be used in the trial, whether any special protocol adjustments need to me made to ensure compliance, who will manage source documents at decentralized sites, and what the requirements will be for any trial-specific procedures.

While DCTs may not be suitable for all trial designs, it is certainly true that the majority of trials can benefit from virtualizing one or more trial components. Prior to embarking on a DCT, it is highly advised that sponsors gain familiarity with the different DCT models available, including their advantages and disadvantages. Ultimately, the model that is selected will depend on the nature of trial protocol and whether HCP visits are necessary. The models range from fully virtual trials to trials that use a combination of virtual methods and site visits. Fully virtual trials, which are currently rare, are conducted entirely off-site using virtual methods for all activities, including consent, and are better suited for trials without complex visits and procedures. By contrast, DCTs that offer a combination of remote data collection (e.g., tele-visits) and clinical site or home visits for protocols that require in-person contact (e.g., complex procedures are necessary) are increasingly common.

There are now several DCTs service providers that have entered the marketplace in recent years, each with different sets of capabilities, including randomization and trial supply management (RTSM), electronic patient-reported outcomes (ePRO), electronic clinical outcome assessments (eCOA), electronic informed consent (eConsent), telemedicine, and sensors/wearables, with each service having advantages and disadvantages. This is consistent with the industry's view that DCTs are a collective list of solutions rather than a single product offered by a company (Medidata, 2020).

Although education and planning are still vitally necessary for adopting and executing DCTs, selecting the best DCT solutions for specific needs will result in positive outcomes for sponsors, sites, and patients.

The ideal solutions eliminate as many disparate hardware and software requirements as possible and provide a unified platform that is user friendly and allows for managing data collected from all the different components of a study in a centrally located source that is available on demand. According to the results of a recent survey, most respondents indicated their preference for platform solutions (having multiple virtual trial components) as opposed to a mix of best-in-class disparate solutions, with more than 80% of respondents indicating that having a cloud-based platform is at least moderately important (Medidata, 2020).

COVID-19 has Accelerated the Adoption of Decentralized Clinical Trials

As noted above, during the height of the pandemic, trials experienced severe decreased enrollment or were halted altogether due to diminished patient ability or willingness to visit sites, delays in trial activities, and difficulties adhering to protocols (Spinner, 2020). This situation forcibly expedited a shift to using virtual methods for many trials, allowing for their continuation and demonstrating the industry's ability to quickly adapt to this new environment in a matter of weeks to months (McDermott, 2020; McDermott, 2021). For instance, in a survey of clinical trial investigators and study coordinators by Xue et al. (2020), it was reported that the percentage of participant interactions conducted remotely increased from 9% to 57% between January 2020 and May 2020 (Xue, 2020). A survey conducted by the Clinical Trials Transformation Initiative (CTTI), a public–private partnership co-founded by the FDA and Duke University,

found that 85% of respondents (a mix of industry, academic, and others) transitioned to remote/virtual visits in one or more ongoing trials during the pandemic (CTTI, 2020); Table 1 shows some of the altered elements. Additionally, a pre-pandemic Industry Standard Research (ISR) survey (conducted in December 2019) reported that 38% of biopharmaceuticals and CROs expected decentralized trials to be a major component of their trial portfolios, and 48% expected to conduct a trial with most activities done in patients' homes. By asking these same questions one year later, McKinsey reported that the responses were now 100% and 89%, respectively (McKinsey, 2021).

Table 1: Pre-pandemic Interactions That Were Transitioned to Remote/Virtual (CTTI, 2020).

Site–Participant Interactions That Changed
Informed consent
Study visits/use of mobile healthcare providers
Safety collection: blood draws, local labs
Endpoint collection: wearable sensors, clinician-reported outcomes, PROs, online cognitive tests
Investigational product shipment
Sponsor/CRO-Site Interactions That Changed
Site initiation visits
Monitoring

These forced adaptations have taught sponsors and CROs important lessons about how trials can be made more virtual in a post-pandemic environment. According to Ken Getz, deputy director of the Tufts University CSDD, some approaches that have been useful during the pandemic, such as virtual trials and remote monitoring, were "already being explored for convenience and will likely continue to see growing use" (Hinkle, 2020), and Ken Getz also noted that this forced shift will likely have unintended post-pandemic benefits:

Regulators worldwide have also been supportive of DCTs as part of the overall clinical trial ecosystem, including guidance on how to incorporate remote features and digital endpoints into trials (see Regulatory section). Lastly, patients have noted satisfaction with the shift to virtual care and communications during the pandemic. In a recent global survey of oncology, cardiology, and immunology patients (including responses from the US, UK, China, France, Germany, and Japan), patients not only reported adopting virtual care and communications at high rates, but 90% also reported that the quality of care was as good or better than before the pandemic, and 60% indicated they wanted to continue using technology in the future for managing their conditions and communicating with their healthcare providers (HCPs) (Accenture, 2020).

> "The forced use of such tech-based modifications to traditional procedures [due to the COVID-19 pandemic] may serve to give sponsors and regulators confidence that they can be effectively deployed in non-emergency conditions."
> - **Hinkle, 2020**

Adoption of DCTs by the Pharmaceutical and Medical Device Industries

The highly regulated nature of the medical product industry has meant that, traditionally, they have been slower to adopt novel technologies, especially in the absence of regulatory guidance. However, there has been a recent upswing in the use of the DCT model, due in part to the COVID-19 pandemic, as discussed earlier, but also due to the growing trend toward more patient-centric trials, the formation of industry stakeholder groups to facilitate collaboration and research (e.g., Decentralized Trials & Research Alliance (DTRA); CTTI's "Decentralized Clinical Trials" initiative) and the possibility of reducing trial time and costs. On this last point, cost savings can arise from a variety of sources, including fewer sites (i.e., less investigator fees and costs for patient visits, and other site costs), less patient travel costs, and less site monitoring and management fees (Clinical Leader, 2019), and according to one estimate, DCTs may reduce costs by 10–25% (Financial Times, 2017). Further, results from a recent survey study showed that from the perspective of sponsors and contract research organizations (CROs), faster patient recruitment followed by overall lower trial costs and improved patient compliance were considered the top benefits of DCTs, and that over the next 18–24 months, it is anticipated that risk-based/remote monitoring and ePRO are expected to be used in at least 50% of trials (Medidata, 2020).

Overall, a confluence of factors is driving the rising adoption of DCTs, including the following:

COMPETITION FOR PATIENTS LIMITS TIMELY RECRUITMENT.
DCTs can increase recruitment by expanding participation to patients across larger geographic regions, and including those with special needs or busy schedules who might not have otherwise participated in a traditional trial. The patient-centric nature of DCTs also enhances patient retention and engagement and improves patient experiences compared to traditional trials because they are more convenient, can reduce the likelihood of missed appointments, and tend to inspire more engagement and dedication in patients. Indeed, the results of a recent industry survey indicate that 80% and 75% of respondents view DCTs as having a positive impact on patient recruitment and retention, respectively (Medidata, 2020).

REGULATORS ARE INCREASINGLY RECEPTIVE TO DIGITAL HEALTH TECHNOLOGIES.
Regulators, such as the U.S. Food and Drug Administration (FDA), are increasingly focused on the patient perspective in clinical trials and real-world evidence (RWE) to help evaluate treatment effectiveness. Digital initiatives and guidance documents collectively suggest that DCTs will play an increasingly important role in the future of clinical trials. For instance, in their draft guidance on heart failure, the FDA explicitly discussed the use of accelerometry as a novel endpoint that will be considered a measure of heart failure and to assess the effects of treatment (FDA, 2019a). Further, industry survey data suggest that regulatory acceptance is a major driver of the increased speed of DCT adoption (Medidata, 2020).

DATA-DRIVEN VALUE DEMONSTRATION OF NEW THERAPIES.
In an environment of pervasive rising drug and device costs, bolstering value demonstration is critical for attaining sustainable drug development in the future, especially in an environment where value demonstration is becoming a greater focus for stakeholders across the healthcare enterprise, including regulators, payers, and patients. Digital tools and methods, both core to DCTs, are modernizing clinical trials by combining complementary data streams, such as subjective PRO data, with objective data arising from sensors/wearables, for example. These combined data streams provide novel insights by yielding highly comprehensive patient profiles that were not readily obtainable in the past.

THE COVID-19 PANDEMIC HAS BOOSTED DCT ADOPTION.
As discussed earlier, the pandemic forced many sponsors to rapidly incorporate virtual elements into their trials, such as technology-based interventions aimed at reducing on-site monitoring visits and in-person patient visits (to minimize potential viral exposure and spread), including telemedicine, remote electronic medical record access for monitors, and virtual monitoring of data and study documentation (Upadhaya, 2020).

> "New streams of real-world data (RWD) gathered from electronic health records (EHRs), lab tests, wearable devices, insurance claims, and even social media can provide important evidence on product safety and effectiveness in settings or populations that may be very different than the information gleaned from registration trials used for approval."
> - **Remarks by Scott Gottlieb, MD as prepared for the Bipartisan Policy Center Conference.**

Precedent has been established for DCTs, such as Pfizer's REMOTE trial (US), Sanofi's VERKKO trial (Europe), Janssen's mSTOPs trial (US), and others, including but not limited to those described by Shore et al. (2019). Initiatives such as CTTI's "Decentralized Clinical Trials" and the DTRA are also paving the way for increased adoption of DCTs. For example, CTTI launched a multi-stakeholder DCT project to provide recommendations on addressing the actual and perceived legal, regulatory, and practical challenges within DCT design and conduct (Apostolaros, 2019) and the project has identified several perceived and actual barriers to DCTs and developed specific recommendations to overcome them (Table 2):

Table 2: CTTI Recommendations and Considerations for Virtual Clinical Trials.

Table recreated and adapted from Apostolaros, et al. (2019). Legal, Regulatory, and Practical Issues to Consider When Adopting Decentralized Clinical Trials: Recommendations from the Clinical Trials Transformation Initiative. Ther Innov Regul Sci 54, 779–787 (2020). Available here: https://link.springer.com/article/10.1007/s43441-019-00006-4. Used under Creative Commons Attribution 4.0 International license: https://creativecommons.org/licenses/by/4.0/

Approaches and Protocol Design	• The design and implementation of DCTs does not have to be an all-or-nothing approach. Use a partially decentralized (hybrid) approach if applicable. • Engage all stakeholders early and often. • Implement fit-for-purpose designs; proactively address and map data flow and communications. • Partner with those experienced with telemedicine.
Telemedicine State Licensing	• Maintain an investigator in each state in which the DCT is conducted. • Utilize investigators licensed in multiple states; contract with qualified mobile HCP research services. • Consult appropriate experts regarding telemedicine laws; seek reliable legal expertise and/or partnerships.
Direct-to-trial Participant IMP Accountability	• Consult and ensure compliance with relevant federal and state statutes and regulations. • Clearly describe the investigational medical product procedures in the protocol. • Outline accountable parties at each step of the supply chain in the investigational plan; engage vendors/pharmacies with direct-to-trial participant experience.
Mobile Healthcare Providers	• Consider as a substitute for visits to investigative sites. • Delegate responsibilities consistent with state laws and the protocol and only to qualified personnel; consider consulting/partnering with a mobile HCP vendor.
Investigator Delegation and Oversight	• Hold to the same standards as traditional trials. • Define "routine care"/ "practice of medicine" as opposed to "clinical-trial-related activities" clearly in the protocol. • Evaluate local and/or mobile HCPs' roles in clinical trials and in relationship to FDA regulations. • Delegate authority and responsibilities in the same way as in traditional trials. • Consult FDA regulations and guidance when determining whether and how to list HCPs on the Form FDA 1572.
Safety Monitoring	• Hold to the same standard as traditional trials. • Clearly articulate remote safety monitoring procedures and train investigative staff. • Establish record-keeping protocol to ensure compliance; develop protocol-specific safety monitoring and communication escalation plans.

Regulatory Trends

Major regulatory authorities across the world have recognized the increasingly digital future of clinical trials. These agencies are quickly evolving and adapting to the new digital world, as evidenced by the increasing number of digital initiatives, guidelines, and regulations for the safe and compliant conduct of DCTs. In particular, the FDA has long adopted the view that the patient perspective should be built into the drug development process, which is a key value add for DCTs. At the ACRP 2021 virtual conference, an FDA official noted several "actual and/or perceived benefits" of DCTs (ACRP, 2021):

- More efficient clinical trials at lower costs
- Accelerated enrollment and increased diversity
- More frequent measurements
- Reduced time and travel burdens for patients

The COVID-19 pandemic has super-charged changes coming from regulatory agencies across the globe, including the FDA, the European Medicines Agency (EMA), the UK's Medicines and Healthcare Products Regulatory Agency (MHRA), Singapore's Health Science Authority (HSA), and China's Center for Drug Evaluation (CDE). All these agencies have issued guidance documents that describe how new processes and methods can be implemented to protect patients and facilitate continued trial execution while maintaining GCP standards (FDA, 2020a; EMA, 2020; MHRA, 2020; HSA, 2020; Taylor, 2020). These documents cover a variety of topics, and they all contain sections that discuss the use of digital health technologies and how they can be used to facilitate trials during the pandemic, such as enabling remote site monitoring, handling informed consent, conducting remote trial visits, and maintaining data integrity and audit trails. It is important to keep in mind that using sensors for remote assessments does not necessarily require regulatory approval, such as 510k clearance; rather, their use is determined based on certain criteria, such as unmet needs or analytical and clinical validity (FDA, 2019b).

In the US, various FDA initiatives in recent years have provided regulatory guidance for the use of technologies in clinical trials. In 2015, the FDA sought input for "using technologies and innovative methods" to conduct clinical studies. Similarly, to fulfill its commitments with the 21st Century Cures Act and PDUFA VI, the FDA has exerted significant efforts to advance its patient-focused drug development program. This program is intended to inform how stakeholders can best develop and apply methods to gather, use, and submit meaningful patient experience data to advance drug and device development while maximizing data utility for regulatory decision-making (FDA, 2020b). Further, at the FDA's suggestion, CTTI has initiated a mobile clinical trial program "with the purpose of influencing the widespread adoption and use of mobile technology in clinical trials" (Shore, 2019).

> "Regarding regulatory challenges, Hawkins said she has found regulatory agencies to be quite interested in working collaboratively to implement and pilot these new digital technologies in the context of clinical trials. An important concern, however, is endpoint validation using a specific digital health technology, which requires implementing a time to validate the technology into a clinical development plan"
> - **Kimberly Hawkins, Clinical Sciences and Operations Project Leader Head at Sanofi Genzyme (as quoted in Shore, 2019)**

The European Commission has also embarked on various digital health technology initiatives, including publishing a legal framework that provides legal guidance on European Union legislation to app developers, medical device manufacturers, and digital distribution platforms (European Commission, 2020).

Countries may wish to look to Asian-Pacific countries for best practices regarding their high adoption rates of mobile technologies and mobile health (mHealth) (PharmaIntelligence, 2019). Additionally, the World Health Organization (WHO) found that the Eastern Mediterranean, Western Pacific, and South-East Asia Regions had the highest percentage of countries reporting an evaluation of a government-sponsored mHealth program (a critical step toward eventually forming a regulation) (WHO, 2016). A regulatory sandbox initiative launched by Singapore's Ministry of Health in 2018 (and completed in February 2021) was intended to bring together the views of HCPs and businesses so that the ministry can better support innovation. Major topics were mobile medicine and telemedicine, and the ministry stated that telemedicine "is set to become a key feature of Singapore's healthcare landscape" (Singapore Ministry of Health, 2021).

The evidence is clear that regulators are adapting and evolving to an increasingly digital future. As regulations and policies have continued to mature, the industry has increasingly moved forward confidently to incorporate virtual elements into its trials so that it can reap the benefits that DCTs have to offer.

Opportunities for a More Patient-Centric Experience

Relative to traditional trials, DCTs are patient-centric in design and offer many benefits to patients, including:

- **Greater Convenience:** Patients complete all or some visits in the comfort of their own home; travel is often greatly reduced or eliminated.
- **Increased Trial Access:** Without geographic or travel limitations, patients can enroll in trials outside of their local area, and people who might not have otherwise participated in a traditional trial—due to special needs or busy schedules—may be more willing to participate due to less travel and less time off from work.
- **Higher Satisfaction and Retention:** A patient-centric approach gives patients more choice in their clinical trial experience, which yields higher satisfaction scores and a greater percentage of patients completing trial visits.

Sponsors and CROs should also consider the trend of patients using their own devices (also referred to as "bring your own device" [BYOD]) to enhance patient centricity. By integrating directly elements of a trial into a patient's life, there is a better chance that they will be engaged. Byrom et al. (2018) evaluated patients' preferences for ePROs and paper-based PROs by having them complete a PRO on paper, and electronic format using an app installed on the patients' own mobile phone or a provisioned device. Overall, the investigators found that 94% (146 of 155 participants) indicated that they would "definitely or probably" be willing to download an app onto their own mobile device for an upcoming clinical trial, while 45% stated that BYOD would be more convenient, compared with 15% preferring a provisioned device. Some of the challenges associated with BYOD trials include patients deleting the app, turning off notifications, or losing their device during the trial (Gwaltney, 2015). In some cases, a mixed BYOD/trial-provisioned model might be ideal, allowing patients a choice in their clinical trial experience (Eremenco, 2014).

Challenges Associated with DCTs

Clinical trials are currently being modernized to include more DCT elements, and this increasingly digital future means that biopharmaceutical companies, device manufacturers, and CROs must consider whether their data capture systems are scalable and interoperable for all types of digital technologies and data volumes, ranging from simple laboratory test results, smartphones, and web apps to high-volume, high-velocity data from medical-grade sensors.

Modernized clinical data management platforms are seamlessly uniting features that support patient-centric DCTs, including eConsent, ePROs, capabilities to manage a broad range of wearable/sensor and digital health technology data, telemedicine, patient registries, and patient portals. By leveraging automated and intelligent tools, unified platforms are driving streamlined and automated workflows, and facilitating interaction between all stakeholders in a trial.

Further, at the recent ACRP 2021 meetings, an FDA official suggested the following as some key challenges that need to be worked out regarding DCTs (ACRP, 2021):

- Consistency in protocol execution
- Data reliability and integrity
- Immature digital infrastructure in some parts of the U.S.
- Perception of regulatory barriers
- Highly varied state laws and regulations

Notably, at least some of these common challenges can be overcome by leveraging unified platforms, as described above.

Summary

DCT designs are being adopted at an accelerated pace, and the trend is being driven by several headwinds that have converged, including the COVID-19 pandemic, ballooning drug development costs, and a greater focus on the patient-centricity and value demonstration of new therapies.

Clinical trials are currently evolving and becoming modernized as they continue to integrate more and more virtual elements. Sponsors must prepare themselves for this increasingly digital future, which will demand scalable, flexible, interoperable, unified, and intelligent software platforms to synthesize patient-centric data into real-time insights that will offer benefits to stakeholders across the healthcare spectrum.

To learn more about how Medidata can maximize the success of your DCT, please visit:
https://www.medidata.com/en/products-virtual-trials/

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