FLETCHER SPAGHT, INC.

Spotlight on Decentralized Clinical Trials

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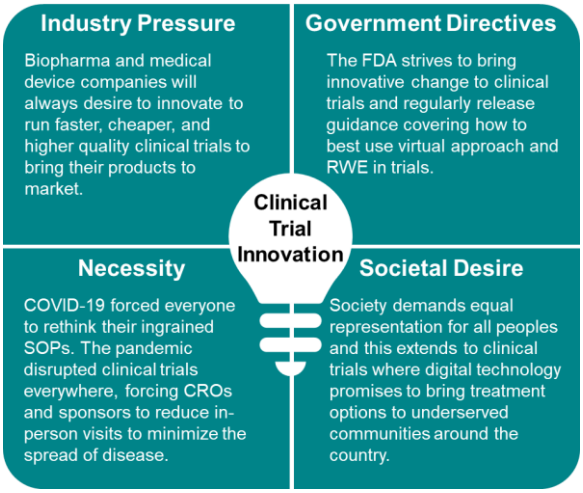
Benefits of DCT Driving Accelerating Growth / Utilization

The Covid-19 pandemic forced society to rethink "operating procedures," and clinical trial sponsors were no different. Recognizing the gravity of the situation, the FDA quickly released temporary guidance for navigating clinical trials during the pandemic, urging sponsors to use decentralized* clinical trial (DCT) methodologies to reduce risks associated with in-person contact while maintaining patient care and study continuity[1]. As a result, conversations around decentralized clinical trials increased substantially (Figure 1). This new urgency served to accelerate the longer, slow-burning trend towards trials utilizing decentralized methods and real-world evidence (RWE). Over the past decade, use of DCT approaches has increased dramatically. In 2010, about 150 trials employed virtual methodologies, by 2019 the number more than doubled to 451, and by 2021 it had jumped to 670. The FDA has kept abreast of this trend, releasing guidance on their thinking roughly every year since 2016.

Figure 1: Clinical Trial – Imperatives for Innovation



Decentralized clinical trials have the potential to alleviate some of the most pressing hurdles the industry faces while simultaneously providing accurate, more complete information. In this discussion, we assess the magnitude of current trends, identify how industry leaders are getting involved, and identify where these methods are most likely to be successfully supported by the FDA.

Decentralized, Virtual and RWE Tools have the Potential to Transform Clinical Trials

Clinical trial pain points are well-known and add substantial cost to trials each year (*e.g.* slow patient recruitment and high dropout rates). An estimated 20% of trials are terminated due to low recruitment and more than 19% of participants drop out of trials before completion, expanding timelines and raising costs[2,3]. Decentralized tools address these issues. A recent joint study between Tufts and Medable estimated DCT methods may provide a return on investment of 5x for Phase II trials and up to 14x for Phase III trials; a BCG report estimated that the use of RWE could save $10-20M per trial[4,5.]

* This article uses the definition for decentralized clinical trial methodologies as defined in the 2021 FDA draft guidance "Digital Health Technologies for Remote Data Acquisition in Clinical Investigations" which states decentralized clinical trials are investigations where some or all of the trial-related activities occur at a location separate from the investigator's location

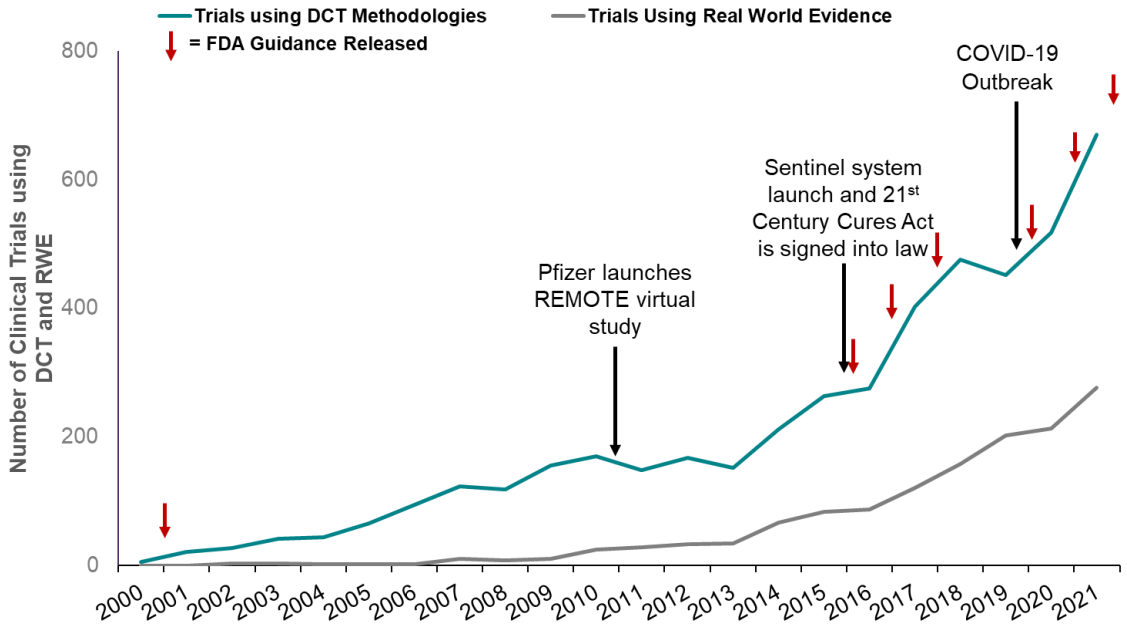
These benefits are not just hypothetical. A recent analysis of DCTs managed by IQVIA showed positive benefits across 14 metrics analyzed, including a 15% reduction in dropout rates, a 39% reduction in screen failure rates, and a 78% reduction in recruiting time[6]. IQVIA expects an enormous increase in DCTs through 2025 and notes that most DCTs will likely follow a hybrid model where some, but not all, trial elements will take place outside of traditional trial sites. Not all trials will benefit equally from decentralized methodology, according to IQVIA, and planning for the use of these methodologies early in the process is likely to yield the greatest benefits.

To date, the FDA has approved over 159 drugs or biologics that used real-world evidence in their submissions[7,8]. These trials used a variety of types of RWE, including retrospective natural histories, baseline controls, published research data, and published clinical data. DCTs that use external controls and have a designated status such as breakthrough therapy, orphan status, fast-tracked, or exceptional circumstances may be especially likely to succeed[9]. A study, for instance, showed that between 2005 and 2017, 98% of clinical trials for hematological conditions, hematological cancers, stem cell transplantation, or rare metabolic conditions which leveraged RWE were approved by the FDA[9].

Clinical Trials using DCT Methodologies and RWE are on the Rise

During the 2000s, pharmaceutical industry use of DCT approaches and RWE expanded at a steady rate; by the end of the decade, about 150 trials employed virtual methodologies and 25 drew on real-world evidence. Adoption soon expanded, and by 2019, trials using DCT more than doubled to 450 and use of RWE saw a nearly tenfold increase to 200 trials (Figure 2). The COVID-19 pandemic served to accelerate adoption even more, driving further jumps in utilization. Adoption of DCT and RWE shows no signs of abating (Figure 2). A 2020 survey of pharmaceutical companies and CROs reported that 71% respondents believed DCT would be at scale or more regularly used by 2024[10].

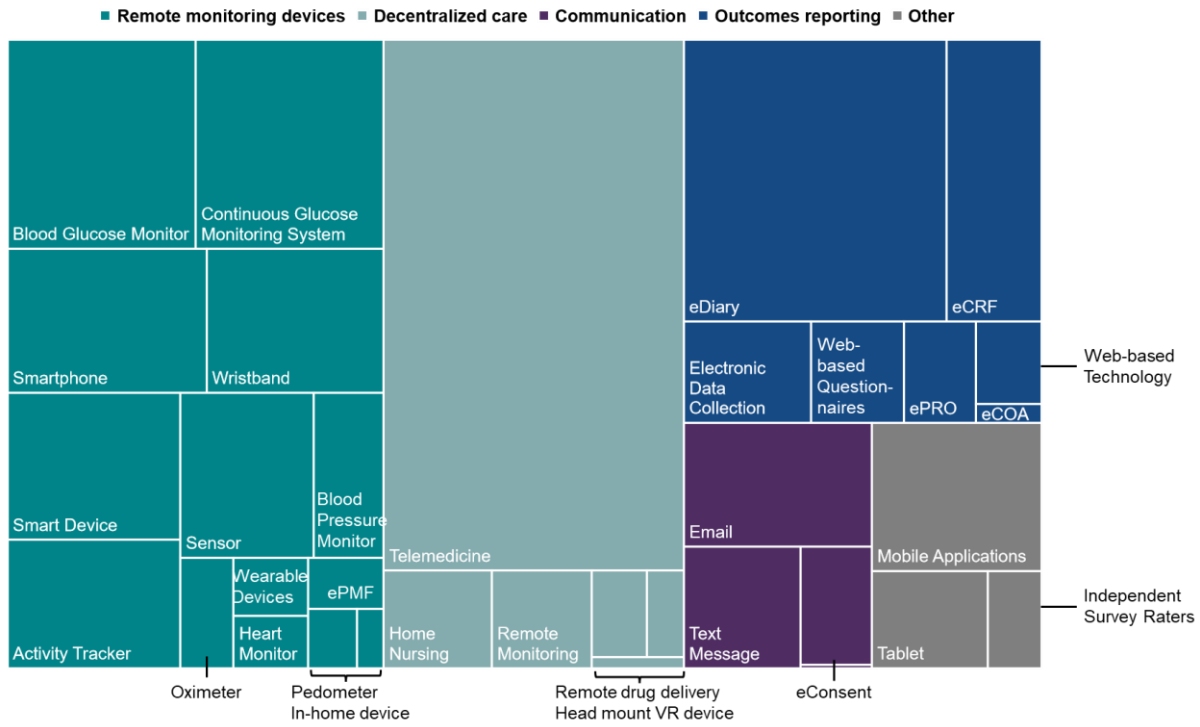
Figure 2: Clinical Trials using DCT methodologies and RWE



DCT Technologies are Better Suited for Certain Functions and Therapy Areas

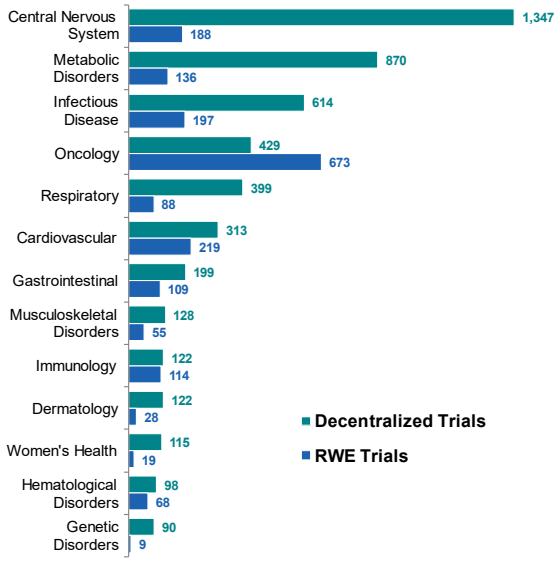
Technologies utilized for decentralized trials include remote monitoring devices, telemedicine, outcomes reporting software, and various communication platforms (Figure 3). Unsurprisingly, the medical devices most commonly deployed include those with high accuracy and well-established histories of monitoring patients outside of the clinic, including glucose monitoring devices, oximeters, and heart monitors. Smart phones and other multipurpose smart

Figure 3: DCT and Virtual Trial Technologies



devices are also used frequently. The lack of complex, expensive, and immovable medical devices underscores the fact that not all clinical trials are suited for decentralization. The ability to remotely monitor and report on patient data depends on available technology. Similarly, some therapeutic areas are likely more suited for these methodologies (Figure 4). An FSI analysis of decentralized trials by therapeutic area suggests that central nervous system and metabolic disorders may be more easily addressed outside clinical sites than other therapeutic areas.

Figure 4: Clinical Trials Using Decentralized and RWE Methods by Therapy Area



Interestingly, there is a striking divergence in the types of therapy areas addressable by decentralized approaches and the therapy areas that are currently using real-world evidence (Figure 4). Oncology trials currently make the most extensive use of real-world evidence. Whether this is a consequence of the availability of real-world data from oncology patients, the limited treatment options for these patients, or the sheer number of clinical trials for oncology, is unclear. The FDA's current thinking suggests real-world evidence may be more appropriate for indications where the progression of the disease is well understood and where not treating control patients with a potentially lifesaving treatment is unethical due to the known severe outcomes they may face.

Industry Players are Enhancing their DCT and RWE Capabilities and Offerings

Given the buzz and potential upside of decentralized trial technology, it is not surprising to see large biopharmas and CROs buttress their decentralized capabilities, as evidenced by recent M&A and partnerships in the sector (Table 1). Venture capital funding in DCT has also seen a marked increase. Since 2018, companies in the virtual and DCT clinical trials space have raised over $1.3B. Three of the largest deals, Huma, Biofourmis, and Evidation Health, have each closed recent financings that raised in excess of $100M.

Table 1. Recent Decentralized / Virtual Deals by Large Industry Players

Company	Type of Deal	Target/Partner	Description
Syneos Health	Acquisition	StudyKIK	Syneos can leverage StudyKIK technology-enabled trial recruiting and retention offering
Syneos Health	Acquisition	Illingworth Research Group	Illingworth provides in-home and on-site research nursing services to clinical trials
Signant Health	Acquisition	VirTrial	Signant Health will now have access to VirTrial's software solution for decentralized trials
Covance	Acquisition	SnaploT GlobalCare	SnaploT offers a number of software solutions for DCT trials such as ePRO, eConsent, eDiary while GlobalCare provides homecare and patient transportation services
Science 37	Partnership	Syneos Health, Signant Health, Novartis, Boehringer Ingelheim	These deals will allow large CROs and Biopharmas to use Science 37's robust DCT software solutions
Bayer	Partnership	Actigraph	This partnership allows Bayer to use Actigraph software and connected hardware in clinical trials for remote monitoring
Pfizer	Partnership	TrialSpark	This partnership opened the door for clinical trial participants to use their primary doctor during the clinical trial rather than participating at the trial site with a trial doctor
CVS	Partnership	Medable	CVS intends to support clinical trials at their clinics nationwide with the help of Medable. This would bring clinical trials to many communities that otherwise may not be capable of participating
GSK	Partnership	Medable	GSK signed a four-year deal to use Medable's DCT components including eConsent, eCOA, and Telemedicine

While many large biopharmas have invested in decentralized trial capabilities and sponsored trials employing decentralized methods, the trend is not universal. At one end of the spectrum, GlaxoSmithKline, AstraZeneca, Novartis, Pfizer and Eli Lilly have each sponsored over 140 clinical trials with protocols including some element of decentralization[11]. At the other end of the spectrum, Bristol Myers Squibb, Amgen, and Biogen have run very few trials using decentralized components.[11]

Regulatory Agencies are Active

The FDA has taken a measured approach to the use of decentralized tools and real-world evidence, supporting its usage and issuing guidance to steer the community on a continuing basis. The FDA has made it clear that DCT methodologies will be held to the same standards for both safety and burden of proof as any clinical trial. In each guidance. the FDA iterates their current thinking on the topic but does not establish legally enforceable responsibilities and does not supersede or limit rules defined by the Code of Federal Regulations.

A recent study confirmed that the FDA is increasingly approving drugs that use RWE during their trials. Of 136 new drugs approved[†] between January 2019 and June 2021, a total of 116 (85%) incorporated RWE, with the proportion increasing from 75% in 2019, to 96% in the first half of 2021[8]. Among the approvals, 88 (65%) used RWE to provide evidence of safety and/or effectiveness. The approved drugs cover a range of therapeutic areas, with oncology, infectious disease and neuroscience the most common by far. In 65 (74%) of these applications, the RWE factored into FDA decision-making; in most cases (65%), the FDA considered the included RWE as supportive evidence, but did classify the RWE as substantial/primary evidence for 9% of these applications. For the remaining 23 (26%) applications, the FDA deemed the RWE inadequate for decision making or did not comment. In some cases, the FDA provided feedback, noting issues with the RWE such as lack of comparability to the current study, differences in end points, and differences in standard care amongst the control groups.

Conclusion

The COVID-19 pandemic highlighted the need to rethink and update clinical trials, adding urgency to the trend to leverage technology and adopt more innovative approaches. The use of RWE and decentralized trials form the core of clinical trial innovation and modernization. Early adopting trial sponsors and CROs are realizing benefits in improved recruiting and retention rates, and, ultimately, lower cost, and faster trials. Likewise, the FDA is clearly signaling its acceptance, both in terms of regularly issuing guidance covering new technologies and developments and also in incorporating RWE in approval applications. With the potential to transform clinical trials, industry participants need to plan early and give careful consideration to how they might identify and implement technologies and methodologies suitable for their clinical studies. In addition, sponsors, CROs, and other industry players such as clinical trial software companies, remote monitoring device companies, and more must monitor and understand general guidance issued by the FDA and other regulatory agencies.

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FSI is a strategy consulting and transaction advisory firm. We accelerate growth for healthcare and life sciences companies and their investors. FSI has nearly 40 years of experience helping companies and investors with growth strategy, business planning, investment diligence, and fundraising.

[†] Includes core drug approvals only – those for new molecular entities or new indication or claim applications. Does not include new formulations, combinations, etc.

Highlights for Key FDA Guidance Related to Decentralize Tools and RWD/RWE

FDA Guidance: Use of Electronic Informed Consent[13]

eConsent is defined as electronic systems or processes that use electronic media to convey study information and obtain and document informed consent. This guidance covers the use of eConsent for both medical devices and pharmaceuticals and provides recommendations on how to ensure the rights, safety and welfare of human subjects. It also covers how to facilitate the comprehension of information given during the eConsent process, how to ensure documentation of consent is obtained, and how to ensure the quality and integrity of eConsent data.

FDA Guidance: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices[14]

If used correctly, the FDA believes that real-world evidence could reduce the cost and time of generating evidence for market authorization and/or post-market studies. This guidance does not alter FDA decision making processes regarding evidence for a device's safety and effectiveness, but does provide examples of how the FDA believes real-world data may be used to support regulatory decisions. The FDA defines regulatory uses for RWE in this guidance:

- Use as a historical or concurrent control
- Support the approval or granting of Humanitarian Device Exemption, Premarket Approval Applications or *De Novo* request
- Support reclassification of a device or expansion of the label
- Conduct post approval studies
- Gather post-market data in lieu of some premarket data

The quality of RWE necessary to inform decision-making may vary depending on the regulatory use of the data (*e.g.* post-market vs premarket). While this guidance does not opine on the FDA's thinking on how decentralized trials may be suitable for some devices based on their classification, there may be differences of note here for sponsors to consider. For instance, on the one hand, Class I devices may not require a trial at all and thus no decentralized trials may be necessary. On the other hand, Class III devices will likely at least require some traditional visits to a clinical trial site due to the higher inherent risk of these devices but monitoring afterwards may be done using decentralized methods.

FDA Guidance: Submitting Documents using Real-World Data (RWD) and Real-World Evidence to FDA for Drug and Biological Products[17]

This guidance addresses submissions of INDs, NDAs, and BLAs that contain RWD or RWE intended to support a regulatory decision regarding product safety and/or effectiveness. The FDA states that applications that use RWD/RWE to support product labeling should specify as such in the submission cover letter. By reporting submissions that make use of RWE, the FDA hopes to be able to better track the usage of RWD/RWE and inform their RWE program going forward. In these cover letters sponsors should include the purpose for which RWD/RWE will be used (*e.g.* to support safety and effectiveness of a product, to support labeling changes, or to support or satisfy post-market requirements or commitments), the study design that will be used to generate RWD/RWE, and the source of the RWD used.

FDA Guidance: E 10 Choice of Control Group and Related Issues in Clinical Trials[16]

This guidance covers considerations for selecting control groups and the ethics, advantages, and disadvantages of the use of external controls. While the FDA is open to the use of external controls, they identified instances where external controls may not be as reliable as traditional concurrent randomized control groups. For instance, they note that historical controls often have worse outcomes compared to similarly chosen controls groups of randomized trials. Given these differences, they suggest a higher standard for effect size and statistical significance may be needed for externally controlled trials. Because of this, the FDA believes external controls are better suited to diseases with highly predictable courses and where treatment causes large changes. Here the FDA suggests using sources of data where detailed information about individual patients exists to maximize the comparability of external controls.

Highlights for Key FDA Guidance Related to Decentralize Tools and RWD/RWE

FDA Guidance

FDA Draft Guidance: Use of Electronic Records and Electronic Signatures in Clinical Investigations under 21 CFR part 11[18]

This draft guidance expands on the 2003 guidance, "Electronic Records; Electronic Signatures- Scope and Application." This guidance covers electronic systems used to create, modify, maintain, archive, retrieve or transmit electronic records and signatures, including many DCT technologies such as:

- ePRO
- Digital applications
- Ingestible sensors
- Telemedicine
- Wearable biosensors
- Implantable electronic devices
- Any other technology that allows for off-site/ remote data capture from patients

In this guidance sponsors will find necessary measures to take to ensure the security and authenticity of the patient data generated from these methods. They will also find many other considerations like when the FDA considers mobile technology to contain source data; what sponsors should consider for audit trails of data obtained directly from the study participant; how sponsors should validate mobile technology, security, and confidentiality of data captured from mobile technology; and what training is required for use of the mobile technology.

FDA Draft Guidance: Digital Health Technologies for Remote Data Acquisition in Clinical Investigations Guidance for Industry, Investigators, and Other Stakeholders[15]

Digital health technologies discussed in this guidance include software and hardware, including general purpose technology such as smartphones. The FDA believes remote monitoring with digital health technologies has many advantages over traditional data collection at the trial site including more frequent or continuous monitoring, more direct data collection from the participants, and more feasible collection from participants who may be unable to report their experiences. Here the FDA offers recommendations on the selection of digital health technology, the verification and validation of digital health technologies, the use of digital health technologies to collect data for trial end points, the risks associated with the use of digital health technologies, and the management of risks from digital health technologies.

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