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Decentralized Clinical Trials 'No Longer A Leap Of Faith'

by Vibha Sharma

This second segment of a two-part *Pink Sheet* article on decentralized clinical trials looks at ensuring that staff at study sites are on onboard to support fast-paced change in this field, how regulatory guidance can help tackle hesitancy, and the need to transparently track such studies.

The momentum behind the adoption of decentralized elements in clinical trials, which was kickstarted by the COVID-19 pandemic, is set to grow over the coming years and will make this way of conducting research the "de-facto standard."

"The decentralized clinical trial (DCT) model works and works well," and embracing it is "no longer a leap of faith" for sponsors, said Sanskriti Thakur, chief growth officer at the virtual clinical trials solutions provider, Medable.

Such trials allow some or all study-related activities to
be conduct in or near a patient's home and many leading pharmaceutical companies are expanding their activities in this field.

This uptake is driven by the fact that DCTs can potentially address multiple issues that have long affected traditional clinical trials, such as those relating to "time, cost, and low participation rates," said MaryAnne Rizk, Medable's chief strategy officer.

One area that needs urgent attention and where the industry has made "very little progress" in decades relates to improving diversity among trial participants, noted Rizk. "Adopting technology and solutions that support meeting participants where they reside will improve access, equity, and facilitate more inclusive representation," she told the *Pink Sheet*.

"As we have observed in many other industries such as online shopping, convenience is a driver

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of many sticky solutions," Rizk said. She believes that DCTs are "here to stay" as they can have a "real, sustainable impact" on multiple issues that have long plagued the research industry. (Also see "*How Decentralized Clinical Trials Are Delivering Time And Cost Efficiencies*" - Pink Sheet, 20 Sep, 2022.)

> *"We are living the evolution of clinical trials" – Sanskriti Thakur, Medable*

SANSKRITI THAKUR IS CHIEF GROWTH OFFICER AT MEDABLE

Thakur believes we are "living the evolution of clinical trials." Just as banking consumers migrated to online methods "without even realizing that a major shift was taking place," she said, "sponsors, [trial] sites, and patients will expect digital tools to drive clinical trial performance, superior experience, greater diversity, and better outcomes."

As reported previously, a great deal more activity is expected in this field over the next three to five years, with DCTs being run in many more locations other than clinics and homes, offering the possibility of much wider patient participation. However, there are challenges as well as opportunities. (Also see "*'Decentralized Clinical Trials 2.0' On The Horizon*" - Pink Sheet, 6 Feb, 2023.)

Just how fast things have moved on this front can be gauged from the fact that prior to the COVID-19 pandemic, activity in the DCT space was mostly limited to "incremental experiments," said Craig Lipset, co-founder of the Decentralized Trials & Research Alliance (DTRA), a multi-stakeholder group that took shape amid the coronavirus pandemic to accelerate the adoption of DCTs.

There were no broad commitments from large pharma firms then towards adopting DCTs, noted Lipset. Fast forward to DTRA's annual meeting in November 2022, where Lipset said representatives from major companies, such as Pfizer, Otsuka, Bristol Myers Squibb, Boehringer Ingelheim and Sanofi, took to the stage and spent 20 minutes each describing their enterprise-wide commitment to DCTs and what that meant in terms of their operating model, targets etc.

"It's a remarkable shift from just three short years ago," Lipset noted.

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All Aboard!

But embracing fast-paced change comes with its own challenges, and already personnel working at clinical trial sites in the EU and the US have aired frustration at being faced with an increased burden to support DCTs. (Also see "*Decentralized Trial Technologies An 'Encumbrance' For Site Personnel, US Survey Shows*" - Pink Sheet, 19 Dec, 2022.)

CRAIG LIPSET IS CO-FOUNDER AND CO-CHAIRMAN OF THE DECENTRALIZED TRIALS & RESEARCH ALLIANCE

For this, Rizk blamed the "one-size-fits-all" approach to DCTs taken by sponsors and contract research organizations to speed up the development of vaccines and manage ongoing trials during the pandemic.

It required sites to "use whatever technology" the sponsors/CROs had selected "without fully assessing the burden on sites and study personnel." While this approach helped reduce the burden on participants, "it inadvertently added burden to sites," she said.

There is now greater awareness around the issue as multiple public and private organizations "have served as productive forums to elevate the sites' voice," said Rizk.

Over the past 12 to 24 months, "investigators, clinicians, and study staff were increasingly brought to the table to gain insights on feasibility, complexity, and needed workflow shifts to seamlessly incorporate technology into trials," she added.

> *"Technology has been a growing challenge for research sites for a number of years" – Craig Lipset, DTRA*

Lipset also pointed to the need for change management when faced with new ways of working, saying that "technology has been a growing challenge for research sites for a number of years." This was not driven by DCTs, he said, but he acknowledged that DCTs "can certainly exacerbate" that situation by introducing even more new tools and technologies.

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However, because it was not "acceptable, sustainable [or] scalable" to continue stacking more burden on sites with new technologies, Lipset said the DTRA was looking at initiatives to help sites "by shifting that technology focus, wherever we can, towards minimum quality standards and interoperability."

This means that if a site has an existing platform for electronic informed consent "on which you're already comfortable" and "your colleagues are already trained," the aim would be to help support the site leverage its existing technology platform investments when carrying out DCTs, he said.

No Room For Bullying

Another aspect that needs careful consideration in relation to DCTs is the growing involvement of sponsors in contracting third-party vendors, especially for tasks related to patient safety (eg, home nursing, remote physicians) that traditionally fall within the trial investigator's remit.

This has spurred calls for sites to be allowed more flexibility to choose their own vendors for DCT-related elements, rather than having these imposed on them.

The issue is also addressed in the EU DCT paper, which states that investigators should be able to agree to or decline the use of vendors selected by sponsors for tasks related to the medical care of trial participants.

Lipset said investigators should not "feel bullied or arm twisted into signing delegations of authority," but if they were "feeling that constraint," then appropriate solutions were needed within the research ecosystem.

MARYANNE RIZK IS CHIEF STRATEGY OFFICER AT MEDABLE

Large health systems and site networks, for example, have invested in their own "home health" and "visiting nurse" service capabilities, which Lipset said was "fabulous" and meant that investigators could leverage their own resources if it "gives them a sense of greater accountability, oversight and control over the patient's experience."

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> *"The old 'one and done' era," when 50% of investigators never did a second study, "will end with increased use of decentralized approaches" - MaryAnne Rizk, Medable*

But if external third-party vendors are seen as a "black hole," then the ecosystem should respond appropriately and make sure that investigators have the right tools to support proper oversight, said, Lipset. "Fortunately, we see that well clarified in the European [DCT] recommendations," he added.

As investigators are responsible for the overall well-being and safety of trial patients, Rizk said it made sense for them to be "selective" and to focus on vendors that aligned with their patient-focused outcomes. Digitizing the consent process and other decentralized elements would allow investigators to "reduce administrative activities to focus on the clinical aspects of treating the patient during their visit," she said.

The use of decentralized elements could further help investigators by freeing up time from administrative tasks. "We expect the old 'one and done' era," when 50% of investigators never did a second study, "will end with increased use of decentralized approaches as investigators can see more, do more," Rizk declared.

Not Flying Blind But Guidance Can Help

Regulators across the globe are also evaluating DCTs and their potential benefits to patients, "with a keen eye on security and data privacy issues," Rizk said.

As industry is still in the early stages of adopting DCT elements, "regulatory change along with process and technology change is a must," she said. Firm regulatory guidance would provide sponsors with "greater confidence and assurance," and help instil "greater trust in data generated using DCT methodologies."

While regulators in the EU and the US have taken the lead on developing such guidance, Lipset said initiatives were also afoot in other regions. In Japan, for example, the DTRA has been communicating with the research community, especially in oncology, that is working with the Japanese regulator PMDA on issuing DCT guidance.

More recently, the DTRA began working with domestic organizations in China after the Chinese regulator started drawing up its DCT recommendations. Lipset said regulators in smaller markets such as Israel had made it clear that for now they intended to watch the EU, the US and others

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and would act in a follow-on capacity.

To address possible ambiguities in regulations, the DTRA is also mapping the DCT regulatory landscape to improve transparency and accessibility.

> *Even in the absence of DCT-specific guidance, "we know what we need to be doing" – Craig Lipset*

But even in the absence of DCT-specific guidance, "we know what we need to be doing," Lipset said. And true to this refrain, regulators in the UK, Canada and many other regions have maintained that while they do not have a specific framework or guidelines for DCTs, nothing in their legislation precludes sponsors from undertaking such studies. (Also see "*'A Lot To Consider' For Sponsors Planning Decentralized Trials*" - Pink Sheet, 16 Mar, 2022.)

"When you look at the [DCT] recommendation paper from Europe," there are no "radically different" approaches in there, noted Lipset. It focuses on the well-known requirements of patient safety, data integrity, not adding to the patient's burden, developing risk-benefit plans, and seeking input from patients and investigators into the trial's design.

While there were some parts of the paper that might help in addressing DCT-related aspects such as insurance considerations, others, like ensuring data integrity due to heterogeneous implementation of decentralized procedures, were not new, Lipset said.

In 2020, when most regulators issued guidance on sustaining clinical trials during the COVID-19 pandemic, they all included discussions on conducting certain procedures at home. "All they really did was call out smart ways to make sure you're using existing capabilities, but without any bar being lowered," he noted.

More than a decade ago, when Lipset was head of innovation and clinical development at Pfizer, he designed and helped lead the first fully remote randomized clinical trial under an investigational new drug application in the US.

> *Some "conservative sponsors" might hesitate in adopting DCTs,*

fearing "cultural pullback" – Craig Lipset, DTRA

It involved an approved drug, Detrol LA (tolterodine tartrate), for overactive bladder, and sought to replicate the results of a previously completed Phase IV Detrol LA trial using fully virtual, decentralized approaches in 2011. "Nobody went to jail, nobody was fired, and nobody was harmed in that process" because existing regulatory, ethical and legal expectations in the research ecosystem were followed, he noted.

Lipset acknowledged, however, that some "conservative sponsors" might hesitate in adopting DCTs, fearing "cultural pullback" from regulatory inspectors or individuals reviewing regulatory submissions. This again raises the challenge of change management, not just in pharma companies and at trial sites, "but also with the regulatory authorities themselves" as "they are large complex organizations," he noted.

Some countries, such as Denmark, have tried to address this hesitancy by proactively interacting with sponsors through focused pilot programs, and by issuing high-level focused guidance quite early on. (Also see "*Denmark Tackles 'All Talk And No Action' On Decentralized Clinical Trials*" - Pink Sheet, 12 Feb, 2021.) (Also see "*Denmark Outlines Vision For Decentralized Trials Beyond COVID-19*" - Pink Sheet, 7 Jun, 2021.)

DCT Trial Registry Coming Up

While the clinical research space is abuzz with talk on DCTs, it is difficult to gauge just how many trials have incorporated decentralized elements in the last few years.

While initially there were some "overzealous marketing claims" by providers of remote/virtual solutions, Lipset noted that some groups have now started making claims about numbers of trials including DCT elements.

However, there is no clarity on how they are sourcing that data" or what definitions they are using" for DCTs, he said. "If they're relying heavily on scraping information on clinicaltrials.gov, we know that most sponsors don't list these attributes" there, he added.

To address the issue, the DTRA created an online glossary on DCTs, undertook surveys for evidence generation, and is now scoping out with member organizations ways to develop a registry that can be made openly available. (Also see "*Global Coalition Develops Consistent Terminology To Support Decentralized Trials*" - Pink Sheet, 6 Sep, 2022.)

Lipset said most DTRA member organizations were already working to make sure they can track studies in their own portfolios using DCT tools and methods. “If we can help them with their own internal tracking with a tool” that also “enables us to aggregate data on the back end,” then “we can open up [that tracking data] and make [it] available for others,” he explained.

Such a registry could be connected and linked to other benchmarking initiatives. It would “hopefully serve as an important resource,” not just to know how many DCT studies there are, “but how they're performing relative to other similar studies that didn't use these methods,” he explained.