OVER A YEAR AGO, AS THE WHO DECLARED the spread of SARS-CoV-2 a pandemic and countries around the world began to feel the impact of COVID-19, hundreds of clinical trials found themselves slowed or temporarily closed as companies and clinics scrambled to reduce the risks to study participants and staff.

Fearful of infection, patients were no longer willing or able to come to central clinics for treatment or monitoring. And clinical resources once dedicated to studies were redirected to deal with the feared onslaught of infected patients. Although many companies refocused their efforts to address the growing pandemic, they and others also looked for ways to redesign and literally retool their clinical trials, shifting the execution of the studies from clinic-focused to more patient-focused.

No one is likely to suggest that COVID-19 has been a positive thing, but the pandemic has forced people to pay more attention to the potential of clinical trial decentralization.

Organizations describe decentralized clinical trials (DCTs) in different ways, but each definition shares fundamental characteristics of digital resources and patient-local treatment and monitoring.

In a September 2020 whitepaper, for example, the Association for Clinical Research Organizations (ACRO) described DCTs as “designs focused on bringing the trial to the patient by utilizing local healthcare providers, optimizing digital health technologies, and enabling the voice of the patient in order to accelerate medicinal product development, speed delivery of therapies to patients, and create efficiencies across clinical research processes.”

Seeing the impact of COVID-19 on clinical trials globally and recognizing the disparate efforts to explore decentralization, co-convenors Amir Kalili and Craig Lipset launched the Decentralized Trials and Research Alliance (DTRA) in December 2020.

“The traditional approach does not allow us to measure what we really need to measure—what the drug does to the patient’s disease—because you need to monitor it quasi-continuously.”

- Natalia Muhlemann of Cytel

From Kalili’s perspective, a large impetus for building such consortia was the need to share information and reduce the repetition of failed experiments.

“So much of what we do in drug development is working in silos, running the same experiment,” he says. “My belief is if Company A has developed a certain mechanism and they’ve spent a lot of money proving it actually doesn’t work, if they see another company going down that path, they should at least call them up and say: ‘Listen, here’s our experience.’ ‘We’ve spent all this money. We think it’s a dead end. You may not. But I just want to show you what we’ve done so you don’t waste your money.’

The same was true with clinical trials methodology, he argues. Several companies were doing pilots around decentralization with vendors. And yet, there was no clear mechanism to share lessons learned.

“These collaborations, to Amir’s point, are an important part of how we can together drive efficiency and improve our field,” adds Lipset.

“While decentralized trials are on the agenda for so many other initiatives, there had been no other coordinating place just focused on the challenges of decentralized research,” he explains. “And so, one of the cornerstones for DTRA is to build collaborations with what we’ve identified as over a dozen other consortia and collaborations that had some initiative around decentralization but are otherwise isolated.”

Another mission for DTRA is simply to inform the industry about the availability and opportunities of a decentralized approach to clinical trials.

“I can’t tell you how many people I connected with in last year for whom decentralizing their trial was an epiphany,” recounts Lipset. “I have an infographic I share online, a 17-year history of work in this field, where new stakeholders here get the advantage of standing on the shoulders of their predecessors.”

“But they need to know that they were here,” he continues, emphasizing that driving education and awareness is a priority for DTRA, as well as leveraging best practices and ensuring everyone understands the work done to date.

Lipset is well-placed in that history of decentralized trials as, during his days at Pfizer, he helped design and run the REMOTE trial in 2011.

“Even a decade ago, we were able to demonstrate that from a technological perspective, from a regulatory perspective, these approaches were feasible,” he recounts. “Nobody was fired. Nobody went to jail. Nobody was harmed in the execution of that study.”
“If you think about your traditional oncology study, a lot of those medications are being delivered via infusions, which take hours and lots of careful monitoring of the patients,” says Marina Acosta Enslen of Pho. “So obviously, we’re not going to be able to move to a decentralized model very easily with those types of studies.”

She likewise points to procedures like spinal taps or radiology that clearly cannot be performed in a fully decentralized study. Covance’s Kamal Saini and colleagues echoed this sentiment in a perspective on oncology clinical trials published in JCO Global Oncology.

“A fully virtual trial is not feasible for most cancer studies, given the need for detailed and often delicate discussions, especially at the time of informed consent; intravenous drug administrations; medical imaging; and toxicity surveillance,” the authors suggested. “However, decentralizing some elements when appropriate could make conventional trials more efficient, potentially reducing patient burden and consequential clinical trial dropout and optimizing healthcare resource utilization.”

Lipset warns against making too many assumptions about DCT feasibility at the outset. "A founding member of DTRA is Stand Up 2 Cancer, and there are many that might have thought this is not something you could do in oncology," he notes. "And yet, they’re running exactly that—an at-home oncology trial and with chemotherapy administered in the home."

“So, it really is less of a therapeutic area challenge and one of

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One significant opportunity with taking a hybrid or decentralized approach is the possibility of diversifying the participating patient population. “In recent years, when you look at the drug snapshots data that the FDA publishes on medicines when they are approved, that was a great way to celebrate those who do it right and expose those instances where the diversity is just inadequate,” Lipset reflects. “When you look at the aggregate of that, gender balance has moved ahead light years in recent years,” he adds. “But race/ethnic distribution is still as imbalanced as it had been for years, proving that it’s a particularly vexing challenge that needs fresh approaches to drive change.”

From PPD’s experiences in the United States, says Morton, 30 to 60 percent of participants in trials that incorporate some degree of decentralization are from communities of color. Contrast that with traditional centralized trials, he continues, and that percentage drops to 10 percent or less.

And why is that?
“Firstly, socioeconomic status profiles are different in the USA across the different communities of color,” he suggests. “And when you’re asking people to take time out of their work and attend to the travel and time it takes to participate in the trial, then maybe that’s what was driving the type of socioeconomic class that historically has participated in trials.”

“The other is differences in where people seek healthcare and what types of physicians are involved,” Morton adds.

For whatever historical reasons, he explains, the academic medical centers approached most often to participate in clinical trials—whether it is because they house key opinion leaders or focus on certain indications—tend to serve the healthcare needs of a white middle-class population in the United States. Gao sees this as a reflection of the 80/20 rule. “Eighty percent of the clinical trials are probably done by 20 percent of the sites,” she explains. “So, it not only creates challenges for patients but also for the industry, because you rely on a very concentrated number of sites.”

The opportunity for enhanced access to diversity might also extend beyond national borders, although new challenges arise. Giving thought to his more than 20 years running clinical trials, Kalili has seen the field transform from multiple single-country studies to truly global programs running the same study protocols. One challenge of running DCTs globally, however, is understanding the receptivity of the respective regulatory agencies to decentralized methodologies and technologies.

That said, the potential of being able to simultaneously probe the pharmacodynamics, for example, of an intervention in an Asian population and a Europe-centered group cannot be overstated. “Do I think DCTs will expand that opportunity?” Kalili considers. “Definitely.”

Mike Martin, the Clinical Development Service Line leader and a principal at ZS, tempers the diversity conversation with a bit of a reality check. “For underrepresented populations, decentralized elements will help a lot once they’re enrolled,” he qualifies.

If you can’t afford to take a day off work to go to a site, he notes, being able to perform elements of the trial at home or through a local retailer like a drug store will make it easier to stay enrolled in the study.

“But you still have to go back and solve how you get unrepresented patients enrolled in the trials, deal with the trust gaps, and understand the barriers,” he concludes. “You have to make sure you get those other pieces.”

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Technically speaking
As suggested earlier, a key element that enables decentralization is the expanded use of and innovations in digital technologies, such as eConsent, eCOA, and ePRO devices or real-time patient monitoring with wearables and sensors.

For example, last August, Science37 announced it was partnering with ERT (eResearch Technology) to incorporate the latter’s cardiac safety, respiratory, and imaging solutions into its decentralized clinical trials offerings. The cardiac and respiratory components would be implemented during home or telemedicine visits, while the imaging services would be provided by a local-care network, ensuring medical imaging would be available closer to patient homes.

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Many clinical trial sites are most likely to draw participants from middle-class backgrounds, so when it comes to using remote technology for studies and attempting to broaden the patient participant base, issues like internet access and ability to manage the technology become critical.
Any decision to add a digital component to a clinical trial requires careful consideration, suggests Morton.

“The approach we take is very much that of consulting in design process,” he explains. “It’s not just about jamming a technology in, but will this deliver the endpoints and the data quality as well as the patient experience and the physician interaction that we need to be successful in a clinical trial?”

The focus is not just on the technology to be deployed, he stresses, but also on the training and support services needed for the participants. Understanding that requires answers to a slew of questions.

“Where do they sit on the bench? What support package are we going to put in place? What languages does this need to be in?”

“What's the help desk coverage we need?” he continues. “Is that type of help desk support sufficient or do we need more of a concierge service?”

These are questions faced by all technology providers, not just those working in clinical trials.

“We're living in a time now where the technology advances—forget clinical trials; just our day-to-day life—are such that it is not just the core of the technology, but the user experience, the user interface that's become so much simpler, so much sleeker,” Morton explains. “So much investment goes into how to basically make this foolproof. None of us really went on training courses into how to basically make this foolproof. None of us really went on training courses on how to use Zoom.”

“That’s where we try to think about the patient experience as well,” he adds. “How can we minimize training and make it just much more of an intuitive interaction?”

Recognizing an opportunity during the COVID-19 pandemic, DCT specialist Medable had a particularly active 2020.

In April, the company partnered with AliveCor to incorporate the latter’s KardiaMobile6L system into its DCT platform to facilitate safety monitoring with in-home ECGs. The FDA-cleared device eliminates the need for trained technicians or nurses, allowing patients to self-monitor.

The company also launched a new TeleVisit mobile application, co-developed and deployed with PPD, putting the focus on patient engagement and improved experience. At the same time, Saini and colleagues highlighted in their JCO Global Oncology commentary the need to make sure that remote devices don’t alienate certain segments of your patient population.

“It was heartbreaking to hear this patient describe how he has to travel four hours to go to the sites, and sometimes, he has to stay there for long time to complete all these activities. So, I think there’s a lot to be gained by reducing the number of visits ... or reducing the time they have to spend on-site.”

- Fan Gao of ZS

“It is important to ensure that the increased use of technology does not have the unintended consequence of excluding individuals who are unable or unwilling to access that technology, such as the elderly and disadvantaged,” they noted. Moreover, the increased use of technology may be both an opportunity and a threat to increasing clinical trial participation by people in low- and middle-income countries where access to mobile devices may be relatively good but other infrastructure less so.

Acosta Enslin agrees.

“We can help to provide the device, but we may not be able to provide the access, such as internet access,” she acknowledges.

In part, wearables are becoming increasingly important to clinical studies, says Natalie Mühlemann, vice president of strategic consulting at Cyteal, because they potentially fill a gap where traditional measurements are limited. She offers the example of neurological diseases like multiple sclerosis and Parkinson’s that do not progress steadily but can instead be quite on and off.

“There are days where patients are better and days where they’re worse,” she explains. “The problem with the traditional way, when you rely on periodic visits to the clinic, is they actually don’t give you much information. On this particular day, the patient might feel really great or really bad, and for the whole week or month before, that was not the case.”

Over the years, people have done those validation studies to move away from a paper questionnaire to an electronic version or so forth,” he continues. “So, that pathway was already there for us. It was really just augmenting that endpoint collection with this type of remote visual interaction rather than the people being in the same room.”

For other mobile technologies, such as wearables, devices, and sensors, he contrasts, the work to validate the endpoints and gain regulatory acceptance is ongoing.

Mühlemann sees significant opportunities for getting better data using wearables.

“One of the risks when we start relying only on the patient-reported endpoints or outcomes is that you have a lot of subjectivity,” she says. “My threshold for pain is probably different than your threshold of pain. My quality of life impairment is very different than my neighbor’s quality of life impairment.”

Still, Mühlemann sees significant opportunities for getting better data using wearables.

“[It is] important to ensure that the increased use of technology does not have the unintended consequence of excluding individuals who are unable or unwilling to access that technology, such as the elderly and disadvantaged,” they noted. Moreover, the increased use of technology may be both an opportunity and a threat to increasing clinical trial participation by people in low- and middle-income countries where access to mobile devices may be relatively good but other infrastructure less so.”

For other mobile technologies, such as wearables, devices, and sensors, he contrasts, the work to validate the endpoints and gain regulatory acceptance is ongoing.
The risk with a completely decentralized trial, she continues, is you don’t know for certain that it’s the patient who’s providing the data. Mitigation strategies are in development, however.

“You can have two-factor authentication,” she explains. “They must have certain passwords to get in, and you’re authenticating that it’s them.” She also notes the use of facial recognition software and video monitoring of the trial participant taking the medication.

“But that is one concern that people have,” Acosta Enslen acknowledges. “If you send it out and it’s direct to the patient, then how do you know 100 percent that it’s actually the patient you’re studying who’s using it?”

Another challenge of using a multiplicity of digital devices is their ability to work together on the back-end—the data acquisition hub.

“If are data file formats compatible with each other?” Acosta Enslen asks. “Do you have to do some sort of configuration and along the lines, validation to make sure that if it has to get changed into another format or put through SAAS or whatever, it is compatible? And then how does that data play with others?”

This is the importance of a data hub or central database, she stresses, into which data can flow from different sources and from which the data can be analyzed.

“If you’re trying to force data from one source and then maybe analyze it in a different program or a different system, sometimes it’s not compatible,” she says.

“So far, I haven’t really noticed that it’s the technology not playing with each other,” Acosta Enslen offers.

To help address these challenges and further augment the range of data accessible to clinical trials, Medable partnered with Datavant in mid-2020 to streamline data integration. The Datavant platform helps link de-identified real-world patient data with their study data to provide greater context for their outcomes. This includes everything from electronic health records, claims, and diagnostics to socioeconomic, behavioral, genomics, and other data.

On behalf of the Clinical Trials Transformation Initiative (CTTI), Duke University’s Lindsay Keohoe and colleagues conducted a survey of potential research participants to get a better understanding of patient preferences and interests in using digital health technologies. They warned about seeing digital technology as a panacea.

“If the use of digital health technology is determined to be appropriate for a trial, technology selection should be based on the requirements of the study and the needs of the intended user population,” the authors wrote in a paper published in Contemporary Clinical Trials Communications. “Furthermore, it is important to carefully weight the impact of any technology-related protocol elements on site staff and clinical workflow against potential benefits, and recognize that digital health technology cannot ‘fix’ a trial that is fundamentally flawed.”

Rather than simply assume that digital technology is better than traditional methodology, they advocated the use of feasibility and/or pilot studies with sites and a representative patient population prior to large-scale roll-out in a clinical trial.

“As a rule, the level of testing should be commensurate with the complexity and novelty of the technology to the research team,” they suggested. “At the same time, it is important to recognize that even simple technologies present a number of potential problems related to their use, maintenance and distribution that need to be carefully assessed.”

Despite these precautions and historic industry risk aversion, the landscape for an interest in DCTs is shifting.

“I think that we were all dipping our toes in and kind of testing the waters of going in a decentralized way,” says Acosta Enslen. “This pandemic has just kind of thrown us into the deep end and forced us to re-examine how we’ve been doing things all along traditional way.”

“I certainly believe this trend will continue after COVID,” echoes Gao. “It’s not a temporary thing.”

**Adapt to adopt**

As much as the elements of decentralized clinical trials—whether fully or a hybrid—have been in development for a decade or more, adoption of these elements has been low and slow.

“When we looked at it over the last six years or so, prior to COVID-19, only a bit over 5 percent of the clinical trials had some flavor or component of decentralization,” recalls Fan Gao, principal of the R&D Excellence team at ZS.

From Gao’s perspective, one reason for this slow adoption may be a perceived lack of regulatory clarity, although she is quick to note that many agencies have expressed an openness to or pilot studies with sites and a representative patient population prior to large-scale roll-out in a clinical trial.

“The idea of clinic-based vs. patient-based or decentralized vs. completely centralized is very much about designating the trial to maximize what you can get out of it. Inevitably, it’s not going to be A or B, but rather some point in between those. As you balance the needs of the study, of the participants, and of the different stakeholders to find that optimal spot, and then make adjustments as the study goes on, the opportunity to learn more from the study cannot be over-emphasized.”

“Once you experience what could have been,” Gao enfuses, “it’s very difficult to turn back entirely to the old way.”