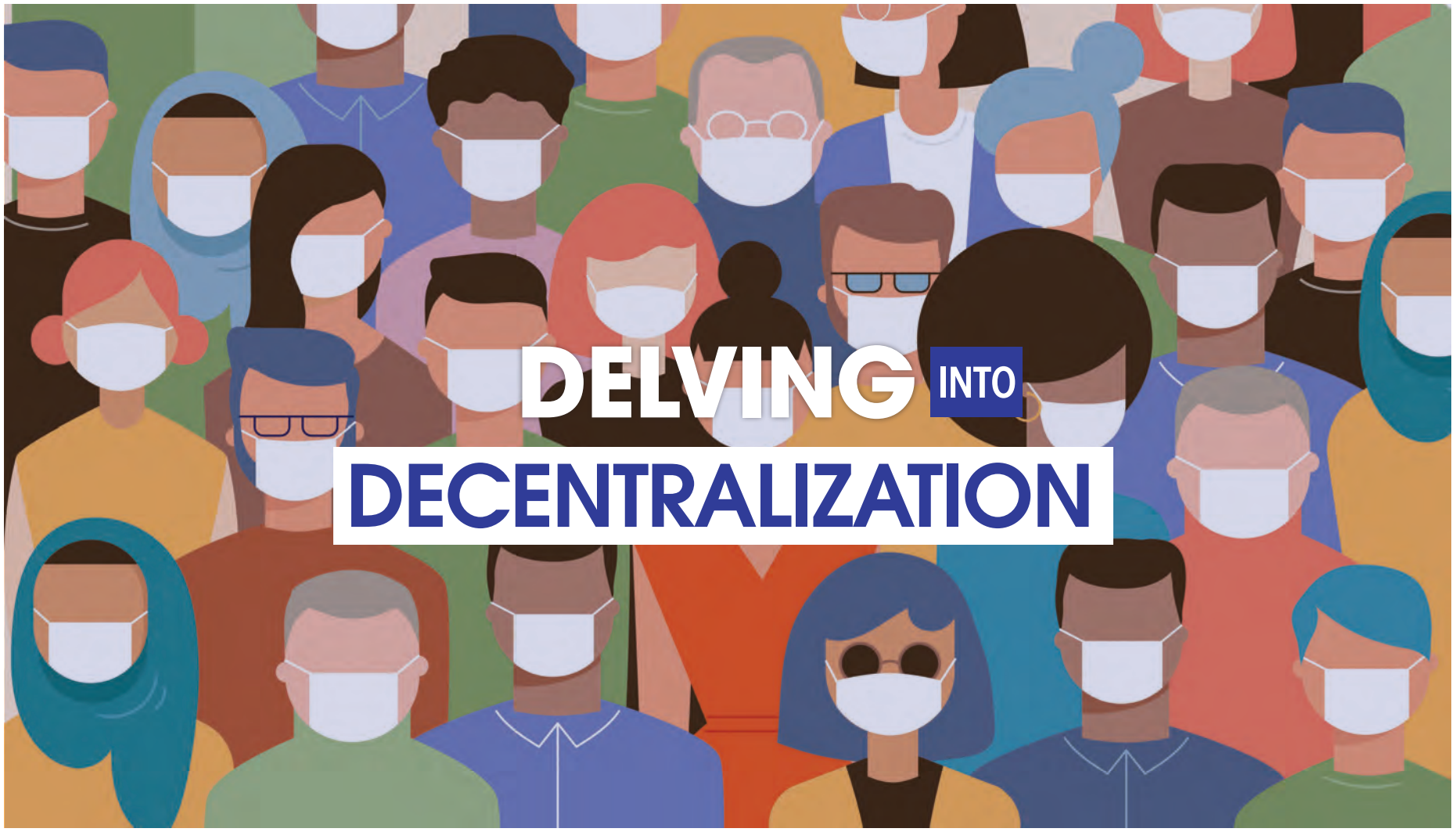
SPECIAL REPORT: *CLINICAL TRIALS*



DELVING INTO DECENTRALIZATION

BY RANDALL C WILLIS

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.

Patients first

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."

Thus, he continues, the barriers to adoption are not in the environment, but rather come from within (see also "Adapt to adopt" article on page 10).

"It's not an epiphany to say that our stakeholders in clinical research are risk averse," Lipset explains. "In many ways, they're supposed to be. This is serious work that's being done, introducing investigational medicines to humans—at times for the very first time—and so there's a reason for risk aversion."

The COVID-19 outbreak inverted that risk environment, he adds, noting, "Suddenly, what had been viewed as risky three months earlier became countermeasures to the real risk. Can I enable continuity for my study when my sites are not able to see patients, when my patients can no longer leave their homes?"

"That certainly was an important catalyst in terms of the role for decentralization shifting from a risky proposition to becoming the risk-mitigation strategy," Lipset presses. "So much of the perceived barrier is now broken down, that perception that I can't do this in my environment for compliance or regulatory or legal or just cultural perspectives."

"A year into this, organizations have seen that they can implement these approaches," he says. "They had to."

Although technological innovations are enabling decentralization (more on that later), the move has been empowered by a shift in mindset.

Historically, says Lipset, any attention life-sciences companies gave patients during clinical trials focused on recruitment, retention, and protocol compliance.

"Those were the three measures that mattered, and anything else just needed to be supportive to those three key performance indicators," he says. "But in recent years, participant experience has risen up as the next key performance indicator around the patient that life-sciences companies are starting to measure and hold themselves accountable to.

"Take that alongside the increased drive for diversity and representation in our trials. This is where decentralized research methods really begin to shine, as a countermeasure that can help open doors for access, convenience, flexibility, and participation."

Fan Gao, principal of the R&D Excellence team at ZS, offers a personal perspective on this opportunity, recalling the story of one particular patient.

"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," she recounts. "So, I think there's a lot to be gained by reducing the number of visits when they complete the activities that need to be done there or reducing the time they have to spend on-site because that's hugely burdensome, too."

Marina Acosta Enslen, associate director of the Clinical Management division at Rho, offers her thoughts on DCTs.

"When I think of a fully decentralized trial, I'm thinking of a completely patient-centric trial where you don't even really have investigative sites," she says. "There's maybe a central site that's set up to be the coordinating PI, and things like that that are kind of helping with the sponsor and/or CRO who's involved."

"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."

Most of the data, however, comes directly from the patient, whether through an ePRO (patient-recorded outcomes) or eCOA (clinical outcomes assessment) device or a wearable, and lab work is performed through home healthcare or via kits where patients can draw samples, which they submit to a central facility.

"That's where we're trying to move, but obviously within our regulatory and traditional mindset, that's hard to fully actualize because you want to be able to monitor where the data is coming from and you want to ensure procedures are being done correctly," Acosta Enslen continues. "And trying to get our heads around that as an industry is a little bit challenging."

One way to deal with that leap of faith is to realize that this doesn't have to be an all-or-none, either-or decision.

"Many people have been taking a hybrid approach, where you're implementing a lot of the technologies and ideas of a decentralized trial, but at the same time maintaining some of our more traditional practices," Acosta Enslen says. Instead of relying on a central hub or site, for example, the study may use multiple sites through which patients are recruited and data is streamed.

"That allows for us to continue to have some sort of monitoring going on, as well, just to ensure that there's compliance with the protocol and those core concepts of [good clinical practice] are being adhered to," she adds.

According to Niklas Morton, senior vice president of the PPD Digital business at PPD, where the trial design, the endpoint collection, the patient's underlying conditions or their underlying engagements with the healthcare setting dictate that a fully decentralized is not feasible, the hybrid design still offers organizations opportunities to minimize—if not eliminate—burdens on the patients.

"Maybe there's one visit out of three that they have to come to the site," he suggests. "Or maybe it's just the initial dose and follow-up. Or maybe there's a screening assessment that's more complex."

The use of a hybrid approach may also allay concerns about therapeutic indications or treatment modalities that may need more intensive interactions between a clinical site and patients.

"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," offers Acosta Enslen. "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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pairing the right protocols with the right decentralized methods."

Widening the net

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."

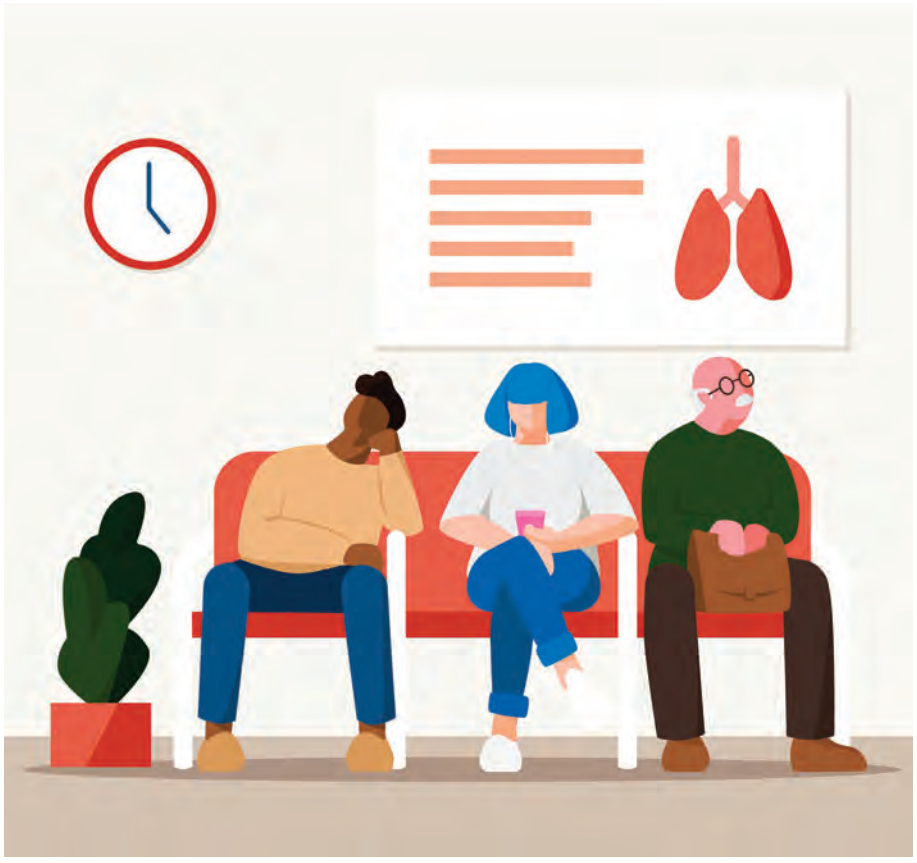
From PPD's experiences in the United States, says Morton, 30 to 60 percent of participants in trials that incorporate some degree of decentralization are from communities of color. Contrast that with traditional centralized trials, he continues, and that percentage drops to 10 percent or less.

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.



"For underrepresented populations, decentralized elements will help a lot once they're enrolled. 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."

- Mike Martin of ZS

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.

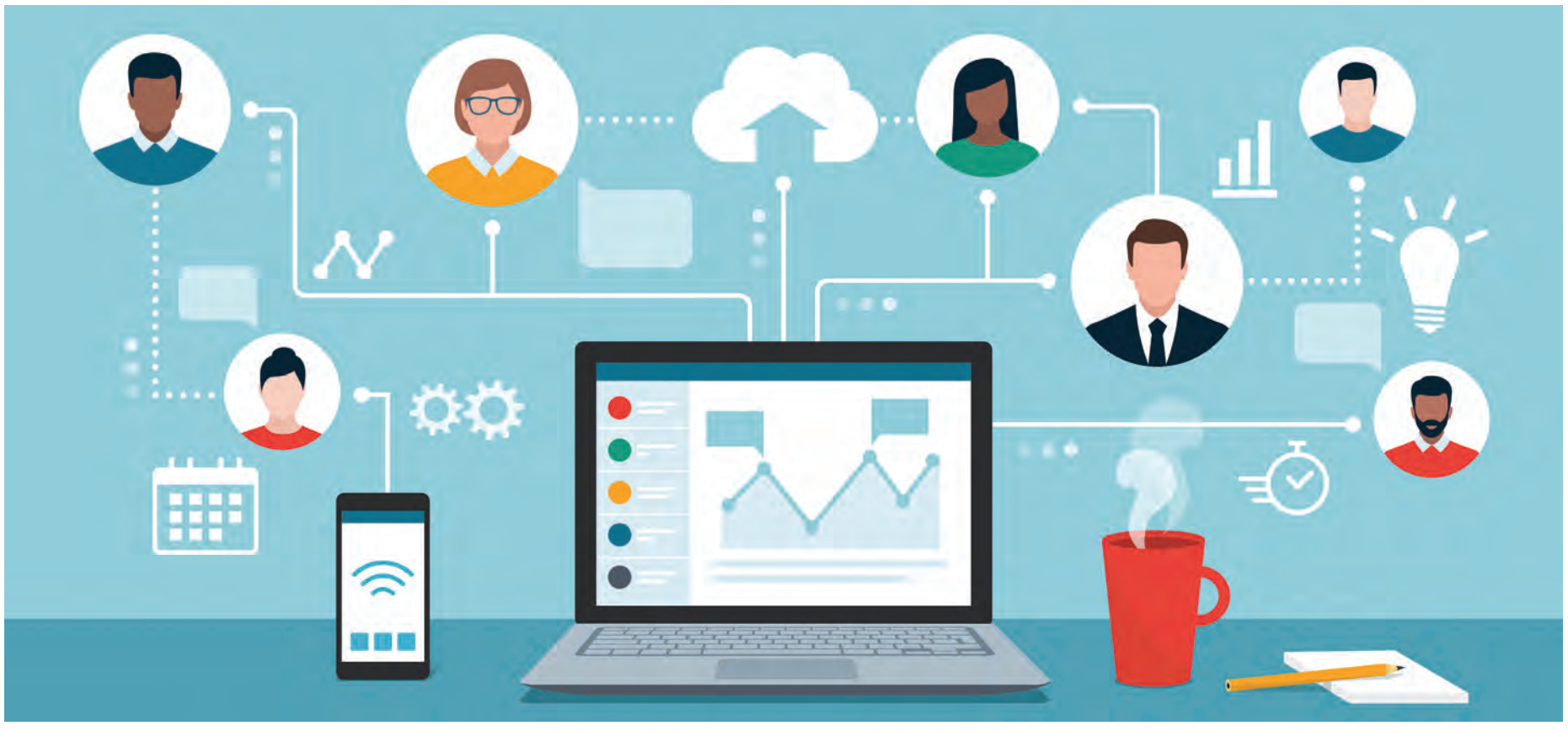
If you can't afford to take a day off work to go to a site, he notes, being able to perform elements of the trial at home or through a local retailer like a drug store will make it easier to stay enrolled in the study.

"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 presses. "So, decentralized elements are going to help a lot, but it's only one piece of the bigger puzzle. You have to make sure you get those other pieces."

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.



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.

Use of wearable sensors and other devices can aid in the advancement and effectiveness of decentralized clinical trials by removing the need for study participants to come into clinics for routine physiological measurements.

Any decision to add a digital component to a clinical trial requires careful consideration, suggests Morton.

"The approach we take is very much that consultative 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.

"We look up front on not just how we're going to collect this data, but what's that experience going to be?" Morton explains. "How are we going to train people? 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 advancements—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 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 Enslen 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 Natalia Mühlemann, vice president of strategic consulting at Cytel, 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."

"So, we need to find another solution, which is not related to convenience or efficiency or COVID, but just by the nature of the disease," she adds. "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."

One challenge of adding digital technologies to clinical trials design is the currently fragmented nature of the digitals and wearables market. Likewise, not all digital technologies are equally well established or fully validated.

"I would say there's a real difference between eCOA, eConsent, and telemedicine vs. maybe these wearables, devices, or sensors," says Morton. "Most of the former were already mechanisms that were used in clinical trials. There was regulatory guidance there."

"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 parses things even further.

"You can go for the medical-grade device," she says. "It's FDA-approved and it's CE marked, if you're talking about Europe. It has been validated that it measures what it claims to measure if you use it within the intended use."

Contrast those with consumer-grade devices that have flooded the market in recent years. There, Mühlemann points out, the bar for clinical research is much higher in terms of assuring the device's reliability, data consistency, and measure validity.

"Because this device has not been reviewed by any regulatory bodies," she explains, "from a medical point of view, a researcher would have a higher burden to actually validate that what you're measuring is really what you think you're measuring."

Still, 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."

"This is very subjective and needs quite a lot of studying," she notes. "That's why wearables are very interesting, because they're basically objective measures."

Highlighting exactly this point in a paper in *npj Digital Medicine*, Georgia Institute of

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Technology's Omer Inan and colleagues pointed to the potential of digital technologies and wearables.

"While many digital biomarkers are still being validated, over time they may provide in-depth information regarding physiological processes central to informing diagnostics, dosing titration and as endpoints for clinical trials," the authors noted.

As examples, they offered wearable sweat sensing for glucose and lactate, as well as electrolytes, cardiogenic chest wall vibrations to assess clinical status of patients with heart failure, and structural health markers for knee joint injury obtained through a brace.

"Harnessing the ability for digital tools to collect data continuously, which can be transmitted directly to researchers, might improve the detection of infrequent events or those that are situation-specific and unlikely to occur during a study visit," they continued. "The speed at which adverse and safety events can be identified and reported may have a significant impact on the timeliness of completion and reporting of clinical trials."

Although remote monitoring and wearables may streamline data acquisition, there still remains the question of verifying whose information is being acquired.

"If a patient's coming into a clinic, you know it's that patient who is using the technology or completing the questionnaire," says Acosta Enslen. "You know you're getting the data from the actual patient, and you know that because the site is doing the research and there's a lot of documentation along the way."

CREDIT: PPD

According to PPD's Niklas Morton, where traditional centralized studies may only incorporate 10 or less percent patients of color, that number can jump to 30 to 60 percent when the trial includes elements of decentralization.

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.

"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 Kehoe 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.

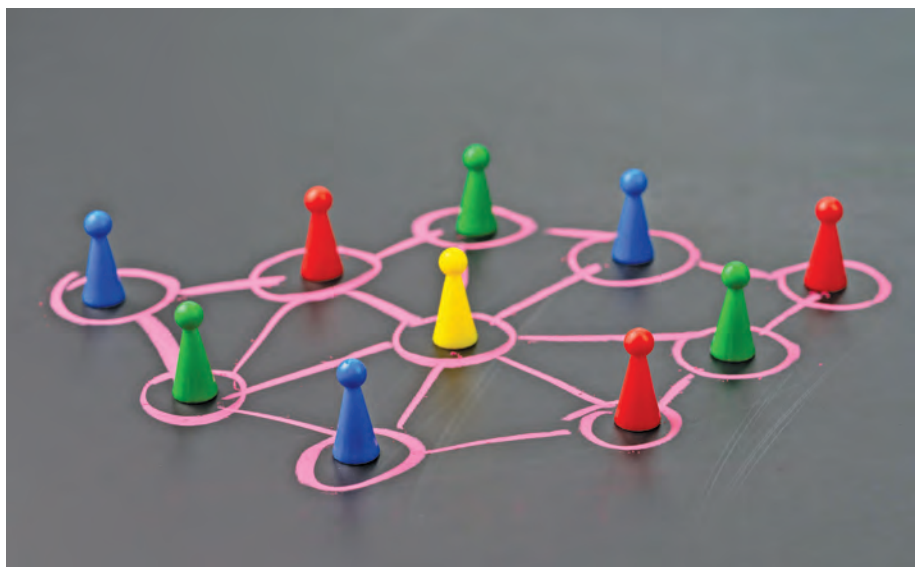
"When we looked at it over the last six years or so, prior to COVID-19, only a bit over 5 percent of the clinical trials had some flavor or component of decentralization," recalls Fan Gao, principal of the R&D Excellence team at ZS.

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 and encourage digital engagement to facilitate access to clinical trials.

"In the US, the FDA has issued a number of guidances on remote monitoring, telemedicine across state lines, shipment of investigative product to patients, etc.," she explains.

A recent whitepaper from the Association for Clinical Research Organizations encouraged early engagement with regulatory authorities when planning a decentralized trial, but also allayed concerns about stricter standards.

The white paper quoted Martin O'Kane, head of the clinical trials unit at the UK's Medicine and Healthcare Products Regulatory Agency (MHRA): "There are [potential] problems in every trial, and just because there's new technology doesn't mean that we have to increase the regulatory burden. So, if they've got something brand new, and they want to incorporate it in a protocol but don't know if it will be acceptable, then they should absolutely come and speak with us."



The bigger issue may be a general state of risk aversion.

"Clinical development is a high-stakes business and so, there is a natural tendency to approach it from what we know and not underestimating what the risks could be," Gao adds.

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>
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Another concern may revolve around the use of remote monitoring and health information security, although Marina Acosta Enslen, associate director of clinical management at Rho, suggests the path has already been illuminated with the widespread use of electronic medical records in clinics and hospitals, at least in North America.

"In the USA and Canada, it hasn't been as big of an issue to be able to look at data remotely, as long as there's a secure portal where the data can be put into," she says. "But my understanding is that there have been some issues in the European Union because they have such strict privacy and health information laws. It has been more of a challenge to look at that data."

The idea of clinic-based vs. patient-based or decentralized vs. completely centralized is very much about designing 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 they experience what could have been," Gao enthuses, "it's very difficult to turn back entirely to the old way." ■