Transformation of Clinical Trial Design and Operations

Interviews with **Science 37**, **Medable** and **Takeda**

Recently, Brittany Erana, MPM, Vice President of PPD® Digital; and Niklas Morton, MSc, Senior Vice President of PPD® Digital, spoke with leaders of Science 37, Medable, and Takeda in an online forum about how the industry is shifting to focus on decentralized trials. They then took questions from attendees regarding their experiences and best practices with decentralized studies.

PART 1
INDUSTRY PANEL DISCUSSION

Why do you believe the industry is just now focusing their attention on decentralized trials?

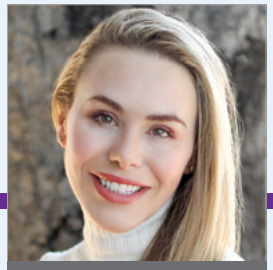
David Coman, Science 37
The benefit of decentralization has always been there, but sponsors have been nervous to take the leap. In today's environment, with limited access to sites, sponsors can't afford not to move in that direction. The decentralized environment has more continuity throughout the patient journey because it's not dependent on sites being open.

Michelle Longmire, Medable
Necessity is the mother of invention and adoption. When COVID-19 hit and sites started closing worldwide, we launched a partnership to keep ongoing trials moving. There's a drive and interest to deliver trials directly to patients. I think we're going to continue to see rapid adoption.

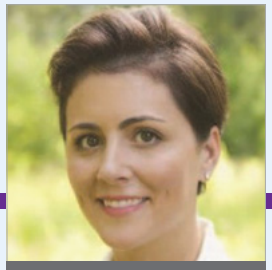
What does a decentralized strategy offer that a traditional model doesn't?

Trinette Mitchell, Takeda
I think a decentralized trial strategy really helps us recognize some of the long-term goals that we've had as sponsors in the industry, which is to extend the reach to patients regardless of their geography. Many sites are far from our patient populations. Our vision for decentralized trials is to expand that reach. From the viewpoint of a sponsor, we can also deploy devices or different types of wearables and that gives us continuous access to data. Maybe there's something in the patient care that's happening off-site that


David Coman
Science 37


Michelle Longmire
Medable


Trinette Mitchell
Takeda Pharmaceuticals


Brittany Erana
PPD


Niklas Morton
PPD

we wouldn't have previously had access to. By looking at that data, we might get more information about the disease state or even identify a digital biomarker that we want to measure. That could propel treatment forward for the solution to that disease state.

David Coman, Science 37
If you look at a world where there's no geographic limits, you essentially get access to any patient anywhere. I think that's the first huge benefit. The second would be enrolling patients faster in a decentralized environment relative to a typical site-based environment. Then it's about being able to keep those patients throughout the trial and the ability to access a more representative and diverse patient population. It's really democratizing clinical research to bring it to everybody. If you look at the current environment, being able to access patients anywhere is particularly important.

> Ultimately, everything goes back to the patient. Instead of thinking about a site as the center of the universe, you start thinking about the patient as the center of the universe and think about how everything extends out from the patient.

Are there specific synergies created by pivoting to decentralized trials?

Trinette Mitchell, Takeda
Telehealth has been an easy thing that we've been able to deploy. And, of course, the change in regulations because of COVID-19 has supported us being able to pivot the way we work. There are more things we need to think about and consider, like removing the brick and mortar site, that we're not ready for yet. But we know everything that we do today is taking us closer to that goal. One thing we do on a regular basis is stay in contact with our patient populations. What's the patient looking for? What is the true burden to a patient in a clinical trial? It may not be what comes to mind for all of us and we're learning that it's different depending on the patient population. We're laying the foundation now to deploy a fully decentralized trial with eConsent and telehealth and supporting our trials with wearable devices.

Is there an increase in data collection or quality that is attributable to running a decentralized trial?

Trinette Mitchell, Takeda
We hope so. As a sponsor, this is always what we're looking for—increased data collection and better quality. We're trying to answer that question by thinking about journey mapping and the patient perspective. Can we understand when they stop entering data? We're also looking at different touch points and incrementally removing pain points that, in turn, will help us have better data collection. Having good technology partners and thinking about how we can streamline the interaction between the patient, the site, and the technology.

Are there other related strategies that contribute to the success of a decentralized trial?

Michelle Longmire, Medable
Clinical trials are a very complex process, but at a fundamental level you have a patient who is looking to receive healthcare from a physician. Sometimes we lose sight of this, but this is the essence of what the patient's expectations are, in addition to participating in an important research endeavor. The key to any clinical trial is delivering the best that healthcare has to offer. Decentralized trials offer convenience and improve access, but patients still want a relationship with the provider and to feel that they're receiving high quality healthcare. It's important to generate that patient-physician relationship and deliver high quality healthcare when using new modalities and methodologies. What we've seen is that telemedicine, and decentralization in general, can facilitate better and more patient-physician interaction, but you must keep communication channels open and provide enough education.

David Coman, Science 37
You've got a whole industry that's spent decades on the site-based model—doing it and always trying to improve. When you think about a decentralized model, you need to look at everything differently. You need to think about the protocol, data integrity, and how to collect the same kind of data that you'd get at a brick and mortar site. You need to think through logistics like direct shipment, nurse coordination, and standard operating procedures. Repetition is important to success, just like in the old model.

Who are the stakeholders that need to be considered in a decentralized trial design?

David Coman, Science 37
We're an industry that, historically, focused on sites as the primary stakeholders. You need to pick the right sites; you need to make sure you have enough sites and think about all the logistics. That paradigm is changing. Ultimately, everything goes back to the patient. Instead of thinking about a site as the center of the universe, you start thinking about the patient as the center of the universe and think about how everything extends out from the patient. It creates a different dynamic where we can work with the patient from the comfort of their own home and make it as easy as possible for them from the very beginning.

Michelle Longmire, Medable
Ultimately, we're delivering healthcare to patients who are part of a clinical trial. Part of that equation is the investigator or the physician, as well as the clinical team delivering care. This new model requires a tremendous amount of consideration for how we deliver care in the patient's

home. How do we collect high quality data and how do we ensure that the providers are well trained? The patient is the primary stakeholder, but you have several additional stakeholders from the clinical team, the sponsor, and the contract research organization (CRO) who are also involved in the study.

Do you see decentralized trials as a short-term solution? Or, as a sustainable, long-term strategy?

Michelle Longmire, Medable

There's been a shift in the way we conduct clinical research. A lot of the conversations around COVID-19 and life sciences and clinical trials have focused on the shift in sponsor adoption, which has been momentous largely out of necessity. But, if you look to the broader trends in healthcare delivery that this has facilitated, it's more of a consumer mindset around technology that's been available for a while even if we haven't adopted it. Look at telehealth and remote healthcare. People are seeing how care can be delivered directly to them conveniently and efficiently. Not only is this a long-term shift born from necessity, it's created an important behavior shift for patients as consumers trying to understand the accessibility and benefits of remote healthcare delivery. I think this is going to lead to a dramatic shift for decentralized trials and patient healthcare delivery in general.

Will the adoption of decentralized trials continue to increase? Do you think this is due to sponsor preference, patient demand, both, or something else entirely?

Trinette Mitchell, Takeda

If we can demonstrate value to both the patient and the sites, that will help increase adoption. I think there is willingness to use technology, so the promise of what that can bring to data collection, and the opportunity to identify digital biomarkers, are reasons why sponsors are interested. I really think it comes down to value and being able to demonstrate it.

Looking ahead, how do you see decentralized trials continuing to evolve? What are other predictions you have and what should we be looking out for as an industry?

Trinette Mitchell, Takeda

At Takeda, our evolution must be holistic. Our internal procedures need to radically change, and we need to look at how we're reaching some of our goals. We all know that we need to collect data, and technology can change how we do that, but we don't need to use the same processes and procedures. How can we reimagine interacting with a patient? How do we change the data flow and still meet all our obligations?

David Coman, Science 37

I think most trials will have some form of decentralization in the future. It's about democratizing clinical research. Studies can't wait for the pandemic to end and patients certainly can't wait. We're in the process of going virtual today.

Michelle Longmire, Medable

As a physician, I think the standard healthcare delivery model leaves a lot to be desired. People want better treatment options. If we collectively execute our vision for decentralized trials, we could make this healthcare delivery model better and more desirable for patients. I see the future of clinical trials as a care option, largely enabled through a decentralized trial approach, where we can deliver new therapies directly to patients.

PART 2

PPD EXPERTS ANSWER YOUR QUESTIONS

What evidence or benchmarks of operational success can you share?

Niklas Morton, PPD

We are continually focused on understanding the metrics of operational success and the value that these types of trials can bring. No two studies are alike, but we're seeing positive trends. The key measures of operational success are patient recruitment and patient retention. In that regard, we've seen the decentralized trial model deliver enrollment rates that are three to five times the enrollment witnessed in the traditional setting. We're also seeing high retention rates, around 90%, which could be 20% to 30% higher than the traditional setting.

There seems to be a lot of considerations and moving parts. How do we get started in developing a decentralized strategy?

Brittany Erana, PPD

There's a lot to think about, but if you identify an internal team to engage with external experts, they can review your protocols and work through simple changes to the schedule to reduce the number of on-site visits and allow others to be conducted at home. As an initial step, you can ask about technology and resources available to support remote visits, considering what it would look like from the patient's perspective. This can help you and your team see where decentralized trial design can bring the most benefit to your organization, indication, and therapeutic area. Getting into the space, workshopping a few protocols, and seeing what questions and ideas surface is key.

How far in advance should we be thinking about or planning for digital trials? Are there situations where it's too late to make the transition?

Niklas Morton, PPD

I don't think it's ever too late, as COVID-19 has shown. When planning for the incorporation of decentralized trial options, earlier is always better. By doing so, it allows you to engage all stakeholders and get their buy-in so you can properly educate and inform patients. For the sponsor who's in the midst of developing a protocol, it's a matter of getting ahead of any obstacles that would impact timelines. With digital enablement, we are seeing data capture happen earlier. Overall, by laying this sort of

groundwork there's an opportunity to have it easily woven into subsequent protocols.

Are there limitations for certain phases of development or therapeutic areas?

Niklas Morton, PPD
This is a really common question circulating in the industry. There are some theories about where these approaches are more established or might be more accepted by stakeholders, like post-approval and observational trials or long-term follow-up studies. However, as a sponsor, it's less about the indication and more about the study design itself and whether or not the center of the trial could be shifted from the site to the patient. If you design clinical trials to mimic the approach that physicians and patients are used to, it's an easier lift.

Is there any difference between the different terms floating around in the industry—telemedicine, TeleVisits, telehealth, remote visits, virtual care, Metasites, etc.?

Brittany Erana (PPD)
Yes, there are some differences and nuances to terms such as "telehealth" and "televisits," but if you're getting started in this space don't worry about the technicalities. You're going to get the point across when you're using these terms in the context of clinical research. They all convey the concept of remote engagement between a physician and patient using fit-for-purpose, video-enabled communication tools.

My organization is evaluating a handful of technology vendors. What criteria is the most important to measure them against?

Brittany Erana (PPD)
Two criteria come to mind. First, look for an integrated platform that offers a seamless experience for patients and site users. Secondly, if you don't currently have in-house digital implementation subject matter experts, or a CRO partner that can support the design and operations, be on the lookout for a tech vendor that demonstrates a strong understanding of your protocol and can explain in detail how their platform will be designed to support it.

How can we assure quality and adherence to regulations when things are changing every day?

Niklas Morton (PPD)
Regulations are certainly changing—or rather, adapting—as the industry evolves in its approach to trials. For instance, we've witnessed regulatory bodies providing updated and timely guidance on decentralized trial conduct. Today, most companies have a process to stay up-to-date with regulations and disseminate information across their organization while ensuring that the processes and study deployments meet those expectations. I know that within PPD, our digital and regulatory teams are aligned and work together to keep our internal knowledge management system up-to-date on elements of a decentralized trial, including regulations on a country-by-country basis.

Are there any incremental steps we can take to help promote hybrid or decentralized trials across our portfolio?

Brittany Erana (PPD)
It seems simple, but one of the initial steps is moving away from paper and increasing electronic options such as eCOA and remote eConsent. These types of options have been around for decades, yet patients are routinely sent home with paper diaries or asked to digitally sign paperwork in an office. Capturing this data both remotely and electronically is one of the easiest places to start. Think about it—whether or not the patient is at the site completing eConsent or hundreds of miles away, a digital signature is a digital signature in both cases. Many of these platforms are 21 CFR Part 11 compliant and adhere to strict data and privacy principles.

Setting a goal for your organization can help shift the mindset from "this is how it's always been done" to "how can we do it differently?" This creates an environment that's more open to the innovation that's required with decentralized trials.

How do I balance the risk associated with the ongoing pandemic (including impacts to traditional models) versus taking on a new, decentralized trial model?

Niklas Morton (PPD)
There's always a chance by remaining unchanged and maintaining your current, traditional protocol, you end up seeing lower recruitment rates across sites as more and more patients become more hesitant to visit sites. This is an incredible risk as it would put research timelines in jeopardy. Historically, teams have been hesitant to "risk swap" and go with a new or novel solution. However, during these times, sponsors have started to see hybrid and decentralized trials as a positive way to reduce risk. At the core of this decision is opportunity cost.

With digital and decentralized trials gaining momentum, does this mean we won't need investigator sites? What does their new role look like?

Niklas Morton (PPD)
At this point, I don't think digital or decentralized trials make investigator sites redundant. Investigators and coordinators are still needed to conduct research and support patients—whether near or far. The reality is that there's no one-size-fits all answer. At this time, we are seeing more hybrid or digitally enabled studies where there still might be some in-person visits needed for key milestones. We are just starting to see the beginning of this evolution, and we are seeing it with healthcare providers as well. So, while more visits may become virtual in nature, investigators, like physicians, will still be needed. Their role is evolving and we will need to see where that goes over time.

> We've seen the most success when all stakeholders are engaged, asking questions and being proactive early on. This helps lay the foundation for success.

How can we make sure patients and caregivers are adequately trained on any new technology and equipped with the right devices? Have you seen a significant learning curve?

Brittany Erana (PPD)

Training a patient or caregiver on the proper way to wear a smartwatch or how to navigate an app is crucial. As with anything new or different, there's a learning curve, so it's necessary to have an education strategy that takes the patient experience into account. There's also a nuance between training and education when it comes to compliance and data quality. For example, we can train a patient how to navigate an app to log a migraine, but it's just as important to educate them on the value of logging that migraine in real time and answering all the questions in their diary, particularly the ones about pain or discomfort.

How you train and educate patients depends on the technology and the patient population. Some patients will do fine with a train-the-trainer approach. Some will benefit from interactive videos or an illustrated guide. It's important to find a partner that can design the education and training program with the patient experience in mind.

My organization has set goals to increase patient diversity for the clinical trials we are recruiting for in the United States. Could decentralized trials help address that?

Brittany Erana (PPD)

Decentralized trials in the United States typically recruit anywhere from 30% to 60% of patients from Black and Hispanic communities, compared to the 2% to 10% that we see in traditional studies. Certain obstacles like access to transportation, the financial impact of taking time off work during standard business hours, and childcare needs can hinder efforts to increase minority participation in traditional trials. A model where some visits can be conducted remotely allows patients to participate from home during non-working hours or on weekends, and this model is certainly a key component of a broader strategy to increase patient diversity in trials.

What recommendations do you have for sponsors looking to engage in design and implementation of such trials for the first time?

Niklas Morton (PPD)

We've seen the most success when all stakeholders are engaged, asking questions and being proactive early on. This helps lay the foundation for success. Identify internal experts and partners to help with the design, operational execution, and technology so you can confidently demonstrate the processes and get people on board.

Are sponsors designing these studies on their own and asking CROs like PPD to implement, or are you designing the studies for sponsors?

Brittany Erana (PPD)

Sometimes we see protocols come in with a "pre-baked" hybrid or decentralized approach and other times we're asked to layer a digital or decentralized strategy on top of a traditional strategy. In the second scenario, a team of consultants will do a deep dive and suggest changes to the protocol to reduce patient and site burden, which technology or device will work best for the patient population, the assessment schedule, study objectives, and recruitment strategies. We've also had sponsors do their own assessment and look to us to validate their approach and optimize the protocol to further reduce patient burden.

How do you incorporate hybrid in oncology trials where some of the visits occur on site with IP delivery? What are your thoughts?

Niklas Morton (PPD)

This is certainly a common question. It really depends on the Investigational Product (IP) itself, the route of administration and the other protocol requirements, such as the need for scans which might require a site visit. In most cases, it's uncommon for sites to need to administer IP at each visit. Patient burden can be reduced using a hybrid model where visits outside those requiring IP administration are conducted remotely. In fact, the most frequently administered oncology drugs tend to be oral. When that's the case there is an opportunity for the patient to participate from the safety of their home through a combination of direct-to-patient (DTP) logistics and remote support from the site. ■

For more information, please contact godigital@ppd.com.

David Coman, MBA, is the chief executive officer at Science 37 and is focused on furthering the company's mission to accelerate biomedical research by putting patients first. In pursuit of its mission, Science 37 makes it easier to participate by connecting patients with doctors and nurses through telemedicine visits and home health screenings, then managing trial logistics from an integrated, comprehensive platform. In an era when 85% of all traditional trials experience delays and capital costs have more than doubled over a 10-year period, Science 37's decentralized model is reimagining biomedical research to get more life-enhancing medicines to patients faster. Prior to joining Science 37, Mr. Coman led the data and analytics business at ERT after serving as the company's chief strategy officer. He also previously worked for Quintiles (now IQVIA) as chief marketing officer and founder of its Digital Patient business. Mr. Coman earned his BA in advertising from Michigan State University and his MBA in marketing, entrepreneurship, and finance from the Kellogg Graduate School of Management at Northwestern University.

Michelle Longmire, MD, is the founder and chief executive officer of Medable. Dr. Longmire is mission driven to accelerate the development of new therapies for disease. As a Stanford-trained physician-scientist, Dr. Longmire identified critical barriers to drug development and founded Medable to pioneer a new category of clinical trial technologies that remove traditional roadblocks to participation and radically accelerate the research process. Medable is now the industry leader in decentralized and direct-to-patient research, serving patients in clinical trials in over 30 languages, 40 countries, and across all therapeutic areas. In addition to having raised over 40 million dollars in venture capital and driving Medable to an industry-leading position, Dr. Longmire has received recognition as a leading innovator and businesswoman, including being named as one of the 100 most creative people in business by Fast Company.

Trinette Mitchell is head of clinical trial innovation at Takeda Pharmaceuticals where she leads a team focused on eClinical trial tools for decentralized trials. With a background in clinical data solutions and partnership management, Ms. Mitchell has a talent for transforming the business process through the implementation of innovative technology.

Brittany Erana, MPM, is responsible for setting the vision and designing the operational infrastructure and capabilities necessary to successfully deliver decentralized and digitally enabled clinical trials while upholding quality. Ms. Erana brings more than 15 years of broad industry experience in global research operations and strategy and digital implementation project and program delivery. She holds a bachelor of arts in psychology from East Carolina University, a master's degree in project management from Western Carolina University, and a certificate in international business from University College Dublin Smurfit Business School.

Niklas Morton, MSc, oversees the operations and delivery of digitally enabled and decentralized/ virtual studies, along with PPD's robotic automation capabilities. Prior to his most recent appointment, Mr. Morton was senior vice president of site and patient access, overseeing the site intelligence and activation, strategic feasibility, strategic site collaboration and clinical innovation teams. Since joining PPD in 1998 as a biostatistics manager, Mr. Morton has advanced through various roles of increasing leadership and responsibility within the company. He earned a master's degree in medical statistics from the University of Leicester and a bachelor's degree in statistics from the University of Glasgow, both in the United Kingdom.