Virtual Trials Offer a Lifeline Amidst COVID, But More than Just Flipping A Switch

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The pharmaceutical industry has been quick to embrace virtual, or decentralized, clinical trials during the COVID-19 pandemic, looking to technology to keep the business of running clinical trials as close to schedule as possible.

Normally, the use of virtual elements in clinical trials would have appeared gradually, rather slowly, as we are part of an industry that likes to consider change pensively. We usually hesitate to move forward rapidly on big issues.

But drug companies have moved quickly this time to salvage their research and at the same time keep patients safe. The FDA has given the green light for initiating virtual trials amid the crisis. The European Medicines Agency has addressed the issue as well.

With a jolt from COVID-19, virtual trials not only are here to stay, but we can expect to see a more extensive use of virtual elements in trials.

Benefits

Virtual clinical trials offer a number of advantages to sponsors. They:

- Quicken recruitment.
- Expand recruitment geographically.
- Improve and expand patient engagement.
- Potentially deliver verified data quickly.
- Are more patient-centric.

With Challenges

However, going virtual isn't as easy as just flipping a switch. Their implementation comes with a number of challenges. The industry has been hesitant because of concerns around patient care, how to collect needed data in a reliable way, and regulatory requirements.

Generally, all virtual and tele-platforms must comply with federal/national and local regulations, including those involving patient privacy. Then, there is a need to establish virtual trial best practices. Protocols must incorporate language that takes into account the use of virtual technologies by both patients and staff.

Staff must be trained in using virtual technologies, and then they must train the patient-device users, unless they can use their own devices, including smart phones and wearable devices. But then these must be validated. Many data acquisition techniques also must be validated for virtual use.

Staff also has to learn how to modify their patient engagement tactics for virtual trials. Home visits by nurses and others can be tricky, especially if homeowners hesitate to let in strangers. Social distancing and mask-wearing recommendations may still be in place. What happens if a home loses power when a medicine needs refrigeration? Usually homes do not have back-up generators like hospitals and clinics.

The differences between traditional and virtual clinical trials are many, as can be seen in Figure 1.

Conventional Clinical Trials Vs. Virtual Clinical Trials

	Conventional	Virtual
Recruitment	Hospital, Advertisements	Web Sites; Apps
Potential Patient Enrollment	Geographically Local	Worldwide
Screening Method	By Phone	Electronically
Study Locations	Several	Few
Patient Visits	In Person	Fewer, Remote-Based
Trial Activities	Personally on Site	Telemedicine Activities
Examinations	On Site	By Remote Visits, Imaging
Testing	On Site	Home-Kits: Local Clinic
Data	Collected on Site by Staff	Collected Through Mobile Devices; ePRO; eDiaries
Medicines	Dispensed on Site	Shipped
Outcomes	Assessed by Staff on Site	Collected Electronically-Digitally
Patient Retentionability	Often High Drop Out	Good Retention Rate

Risks

But virtual clinical trials may not be right for every setting. If a clinical trial necessitates a complex measurement, i.e., brain imaging, a trip to a clinic will be necessary. Those participating in a trial involving gene and cell therapy probably will be required to go on-site for therapy. And there are concerns over the privacy of the data collected. Data collection through an app creates privacy and security risks. Some trials may be hybrid in nature, using both traditional and virtual elements.

The FDA is piloting a new risk-based approach to regulating third-party health data apps. With this approach, Apple and FitBit devices are pre-certified, enabling them to reach market more quickly through an expedited approval process. The FDA values cybersecurity and has published extensive guidelines on the matter.

Virtual trials encourage a new way of thinking and will generate internal challenges. Initially obtaining biometrics data may help with streamlining the planning for the trial. Conducting a risk assessment is a good idea. But while some initial costs may be greater when adding virtual elements, trial sponsors will be paid back in the long term because they add flexibility, cuts time spent on retroactive study changes, and optimizes end of study data analysis.

De Novo Protocols

Many operations are geared toward the traditional site-based model, and use "boilerplate protocols," according to Dr. Jonathan Cotliar, chief medical officer at Science 37, which conducts decentralized trials using an in-house network of telemedicine investigators and home-health nurses supported by a fully integrated, decentralized clinical trial platform.

"You have to create a de novo protocol that accommodates telemedicine and changes to the operational order of the trial to accommodate people participating from home. Those could include sending nurses to the home; shipping the investigational product directly to patients instead of dispensing it from a research pharmacy; and taking into consideration local telemedicine laws that may be different from state to state," Cotliar explains.

"And then you have to use all of those decisions to come up with a protocol that would make it possible to broadly recruit studies in the United States. That may be a tall order for a large organization where a lot is already automated without much thought," Cotliar continues. "So you have to create those documents that are not boilerplate, and they take a lot of time to generate, and require stakeholder approval." A company's time-pressed trial study team may not be incentivized to change the protocol to one containing language for a virtual trial, he indicates.

New Operational Concepts

Sometimes the new protocol language required is not overbearing. For example, instead of indicating that a study could take place only in a clinic, the language could be rewritten to include a patient's home. But one also may have to include completely new operational concepts covering electronic devices, data capture, and telemedicine. These are not significant hurdles, but require more time and consideration than usual, according to Cotliar.

"Not everybody owns the latest smartphone. Not everybody owns or has the ability to buy a high speed monthly data plan. So, if you want to truly democratize clinical research, you have to provision devices to some participants, and buy data plans for them so that socioeconomic status, somebody's ability to own the latest device, or pay for a data plan aren't keeping them from participating in the trial," Cotliar says.

In addition to these issues are concerns over device privacy, HIPAA issues, data security, and standardization and validation of devices and electronics. Also complicating the virtual trial is how clinicians must hold medical licenses in each state that patients reside, just to "visit" them through telehealth, notes Cotliar.

There's little difference between a blood draw in a clinic or in the patient's home, if it's done by a registered nurse with the skill set required to take the sample, Cotliar says. "But for a trial involving inflammatory skin disease, a patient at home would not be assessing skin disease in the same way that a physician would be in a traditional trial. Instead, high-resolution digital photos would be taken and collected," he explains.

"Take, for instance, an oncology trial, where the endpoints are based on a radiological assessment of disease and whether it's stable, improved, or worsened," says Cotliar. "You'd like to have a pre-qualified imaging center obtain those images so that investigator radiologists can review those images.

"In a virtual trial, we'd have the patients go to a local imaging center near their home and have images taken in the same way they would at a pre-qualified imaging center. But instead of a local radiologist rendering a decision, the raw radiology would be uploaded and sent to the trial's oncologist and radiologist for review," he adds.

Circumventing Impediments

"Decentralized virtual clinical trials are exciting, and they offer a huge potential to improve how we conduct clinical research on drug development," says Alison Holland, head of decentralized trials at Medable, a provider of software and digital solutions for decentralized trials. Virtual technologies and methodologies have enabled trial sponsors to circumvent impediments, such as limited patient recruitment caused by geographic location, she explains.

"When we start that conversation with our clients, we want to know about the patients that they are looking to recruit. And then we want to know the type of data that is being sought and collected for the protocol, safety, efficacy, and outcomes. Then, we have to determine how to overlay the data requirements with the patient pathway," Holland says.

It's important to look at a virtual trial from a data flow perspective, and determine what could be a digital source of the data. Then determine how that can be streamed together. And then make sure that the patients have been given choices about how to participate in a secure way, she adds.

Balancing Virtuality and Safety

“But how do we improve our study designs to enable broader participation of patients, and give them more options for how they wish to participate and engage?” she questions. Trial teams must balance the virtual option against the safety parameters of a specific compound, and ensure that the measures they have incorporated into the trial also can keep patients safe at home, according to Holland.

Patient-Centric

“The trial protocol would need to be adapted to reflect the options that patients have. You’d have to modify the assessments, the visit schedule, and the activity that will take place,” Holland explains. “I think as we see protocols going forward, we would see those optional components built in, so that we’re able to share that information with the ethics committees and patients up front after the informed consent process, so that patients understand what their true choices are around the study,” she says.

“Some of the therapies developed in oncology can be pretty toxic, and we’d want to make sure that a patient has as much immediate health support as needed. Maybe they only would have to come on site for a one hour visit instead of a five hour visit. We could still have a good amount of patient activity measured in their homes,” Holland notes.

Extremely challenging would be converting clinical trials in progress to a virtual model, Holland indicates. Sponsors must take into consideration patient safety, health checks, and vital measurements, and then determine how to accurately take measurements virtually. The correct use of digital measurement devices, and patient and caregiver training also must be considered, along with data integrity, reliability, flow, and patient privacy.

Achieving Goals

“For several years, we have been talking about how the confluence of data science, digital health technology, and telemedicine is a potentially revolutionary opportunity for clinical trials in terms of making them better, faster, and less expensive. Virtual trials are now beginning to achieve these goals,” says Dave Hanaman, chief commercial officer and co-founder of Curavit Clinical Research, a provider of decentralized clinical trial services.

The revolution in digital technology makes it possible to measure things in ways that we couldn’t before, and have the data automatically go to the cloud where it can accessible all of the time, he indicates.

Same Fundamentals

“Regulations and protocols have always ensured fundamental things like safety, ethics, and the validity of the data collected. None of these fundamentals change in a virtual or decentralized trial,” explains Hanaman. “What is new is the use of new technologies in

place of older, proven methods, so there is an acute need to spell out in great detail how these new technologies will be leveraged in ways that continue to ensure ethical research, valid data, relevant endpoints, and good outcomes," he adds.

One challenge to the adoption of virtual trials is how many people in the industry are resistant to change, and virtual trials represent a significant departure from the norm. But as sponsors look to continue clinical trials during the pandemic, COVID-19-related concerns for patients' and care givers' safety are overcoming that resistance, explains Hanaman.

Eliminate Bureaucracy

"With traditional trials, you need many patients across many sites, many investigators, as well as genetic, age, and socioeconomic diversity. In traditional trials, this means a sponsor will need multiple sites, and that means complex logistics, duplicative communications, and many researchers across those sites," Hanaman says.

"Traditional trials involve a lot of brick and mortar and very high administrative effort. But a virtual trial can be undertaken with one world-class principal investigator, recruiting patients from anywhere they live, work, or study. You can eliminate layers of bureaucracy, inconsistencies, and logistical complications, and lessen the impact on study participants," he continues. "In this way, you go from being a site-centric to being patient-centric."

Virtual trials help achieve diversity by recruiting patients from anywhere, yielding access to populations who are not geographically near to traditional physical trial sites, or who cannot afford to take time off from work to participate in a trial. And, the data from virtual trials can be collected 24 hours a day in real time, making it valuable for yielding meaningful insights, according to Hanaman.

The protocols for virtual trials essentially have the same objectives, safety, ethics, and endpoints as those of traditional trials. In addition, they incorporate processes that support the use of electronic sources, diaries, consent tools, remote monitoring devices, and real world evidence, Hanaman indicates.

Inclusion criteria and exclusion criteria may differ. Protocols will indicate whether patients can use their own devices, or if they are to be given new devices and trained on them. Protocols also guide how research staff should manage the technology to ensure processes are being carried out consistently, that data is being protected, and that the patients are treated ethically, according to Hanaman.

"They're still going to prioritize good science, good research, patient safety, and ethics," notes Hanaman. "But in addition, you have to make sure that you've got a protocol that spells out exactly how, for example, a 60-year-old person will use a smartphone to collect an electronic patient reported outcome, and make sure the data is valid," he says.

Despite the challenges that must be addressed and changes made, virtual clinical trials are here to stay. As Cotliar says, “Our sense is that once patients get a taste of a more convenient way to participate in clinical research, pandemic or not, they’re going to demand that more studies accommodate them in this way (virtually).”