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# US FDA Outlines Wishlist For Decentralized Clinical Trials

*Companies Need Not Have An 'All Or Nothing' Approach*

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**by Vibha Sharma** | @ScripRegVibha | vibha.sharma@informa.com

## Executive Summary

As interest in conducting remote decentralized clinical trials grows, a senior US regulator explains what companies should consider when planning such trials.


DECENTRALIZED TRIALS HAVE DRAWN PHARMA'S INTEREST *Source: Shutterstock*

Remote decentralized clinical trials have piqued the pharmaceutical industry's interest because of their ability to improve patient recruitment, retention and engagement, while allowing for continuous data capture in real-world settings.

These types of trials are relatively new. In the absence of regulatory guidance on decentralized trials, companies have been experimenting with different approaches to planning and conducting such trials with varying levels of success.

At a recent conference, a senior US regulator outlined various factors that companies should reflect on if they are thinking about conducting a decentralized trial as the approach is not suited to all types of trials.

A key factor to consider is the choice of efficacy endpoints and whether these can be captured remotely, according to the Food and Drug Administration's Cheryl Grandinetti. Objective endpoints such as a serum biomarker or a clinical event like survival or other endpoints that do not require interpretation "may be suited for a fully decentralized trial," Grandinetti said.

Grandinetti was speaking at last month's good clinical practice (GCP) symposium, which was hosted by the UK Medicines and Healthcare products Regulatory Agency in London.

Companies should also consider whether the trial endpoints or any other critical assessments that are obtained remotely can be appropriately validated. This aspect has posed a challenge "with the decentralized trials that have been submitted to the agency for review," said Grandinetti, who is a reviewer in the good clinical practice assessment branch of the FDA's Division of Clinical Compliance Evaluation/Office of Scientific Investigations.

"You should definitely engage with the FDA review division early and often in your planning process," Grandinetti told delegates at the symposium. "In cases where validation of a novel endpoint or one that's obtained remotely via technology has been a challenge, the FDA has been committed to working through these challenges."

Other key factors to consider include looking at the study population and the disease state. "You should look at the investigational product and the treatments used in the trial… It is important to ensure that the study population is stable enough to participate in a

## Box: What Are Decentralized Trials?

Decentralized trials integrate the use of telemedicine, digital health technology tools and other electronic systems to perform some or all study-related procedures at locations remote from the study site.

In a typical decentralized trial, the study subject is located at home or at some other convenient location, while the clinical investigator is situated in a remote location. Such trials mostly involve an electronic informed consent process.

The investigational medicine and other study supplies are shipped directly to the subject's home. Digital health technology tools – such as wearables and systems for collecting electronic patient-reported outcomes – are used to capture endpoint data directly from the study subject and for safety monitoring.

These trials often involve mobile health care providers, who travel to the patient's house to make it more convenient for the patient to participate in the trial. These mobile health care providers are part of the clinical study team and conduct protocol-required study procedures. They may carry out functions such as drawing blood, obtaining medical histories and vital signs, administering the study drug, training the study subject, conducting clinical assessments or evaluating adverse events.

A decentralized trial may also use the patient's existing health care ecosystem (eg, local health care providers, emergency departments, clinics, regional hospitals, etc) to further evaluate adverse events.

trial with remote components," Grandinetti said.

When considering a decentralized trial, the senior US regulator clarified that companies do not necessarily have to go in for an "all or nothing" approach.

In different jurisdictions, decentralized trials are also referred to as "hub and spoke," digital, virtual, siteless, patient-centric, remote and direct-to-patient trials.

"Depending on the trial and the design, you may want to consider a [hybrid decentralized] trial where some activities are conducted remotely, and some activities require the study subject to travel to a designated study site," she said.

Although a fully decentralized approach may be beneficial for some types of trials, most "trials will fit somewhere in the middle of a traditional [randomized control] trial design and a fully decentralized trial," Grandinetti said.

## Special Considerations

Regardless of the approach used, the responsibilities of the sponsor and the investigator do not change, although some aspects considered "routine" in relation to traditional trials may need extra consideration in the context of decentralized trials. For example:

**Subject Safety**: Sponsors should have protocol-specific safety monitoring and communication escalation plans in place, which should describe the role and use of local health care providers to evaluate adverse events. There should be a plan and procedure for after hour emergencies, including information for study subjects on who to contact to address or treat adverse events.

"This is something we would generally do in a traditional trial, but it's particularly important in a decentralized trial that uses local health care providers, who are not part of the study team, to evaluate adverse events," explained Grandinetti. In addition, the trial protocol should describe the electronic informed consent process.

**Study Drug**: Whether the study drug can be shipped directly to the subject's home would depend on various practical considerations, such as the trial's protocol design. If it is a double blinded study, then it is necessary to consider whether the product is already blinded or whether blinding has to be done on site.

Also, one must consider whether the study drug is a stable, ready-to-use compound versus a product that requires reconstitution and has a short expiry date, and whether the drug can be self-administered by the subject.

The drug's safety profile also plays a key role. If the drug's safety profile is well-defined, then it is necessary to consider what the expected adverse events are and whether they require close monitoring, according to Grandinetti. And "can that monitoring be done by mobile study personnel or local health care providers?"

In addition, there should be systems and procedures in place to ensure a patient's privacy when the study drug is being shipped to them. "The procedures for shipping study drugs directly to the patient should be described in the trial protocol so that the process is clear to everyone involved, including the regulators."

**Data Management**: As technology plays a key role in decentralized trials, and because many third parties may handle and store the data, the FDA expects issues relating to data collection, handling and management, and the use of electronic systems to be proactively monitored and addressed by sponsors. "This is a given for all trials regardless of the design, but I really want to reiterate the importance of this in the decentralized trial design," said Grandinetti.

To ensure data integrity and reliability, "you need to have a detailed understanding of the data flow, which may be a little more complex in a decentralized trial than in a traditional trial," according to Grandinetti. She said that companies should have a comprehensive data flow diagram that includes all parties from whom and to whom data are transferred or transmitted, including all third-party vendors contracted for data collection, handling management and/or data processing. "This is a pet peeve of mine, but it would be really nice to see this data flow diagram in the protocol… [or] in your data management plan."

**Electronic Data Capture Systems**: Electronic systems owned by the sponsor should employ necessary data security and integrity controls (eg, access controls, audit trails, encryption and a risk-based approach to validation.) "During inspection, we're going to review your use of these electronic systems in the same way as we would in a traditional trial. We'll focus on those systems that capture the primary efficacy endpoint data and any critical or key data in the trial," Grandinetti said.

The FDA encourages the use centralized monitoring to identify and proactively follow up on missing data, inconsistent data, data outliers and potential protocol deviations that may be indicative of systemic or significant errors. "It really is in your best interest to do this," the FDA regulator said.

Grandinetti recalled a case at the FDA where a sponsor had applied to use electronic patient-reported outcome (ePRO) data to assess the primary efficacy endpoint for a pivotal trial. The agency found that the sponsor had not used a system to proactively monitor any missing data, and later on in the trial cycle, a significant amount of data was found to be missing. The sponsor tried to rectify this by asking the trial investigators to go back to the subjects and interview them to obtain the missing data retrospectively. "Needless to say, this created a major data integrity problem," Grandinetti declared. "Moreover, this was discovered on inspection and was not initially reported to the agency."

**Telemedicine visits**: Sponsor should ensure that internet and wireless technology is available where the trial is being conducted so that study business and assessments can be conducted in accordance with the protocol. Some states in the US have different laws governing telemedicine. For example, they may require that the investigator is licensed to practice medicine in the state where the study subject is located. Some states also require that there is an established doctor-patient relationship for telemedicine treatment and may have different requirements in order to establish such a relationship, Grandinetti said.

**Technical Support And Training:** Technical support is critically important for the conduct of a trial and, quite often, "this is the first place where you might identify faults, validation issues or systemic or significant errors," said Grandinetti. The trial protocol should describe all the training that the study subjects, mobile and local health care providers, clinical investigators and other study personnel will need to use technologies employed in the trial such as electronic systems and telemedicine apps.

# Inspections

As the concept of decentralized trials is still in its infancy, Grandinetti said that the FDA had not inspected any such trial as yet. Nevertheless, she clarified that the inspection process for decentralized trials would be the same as for traditional trials.

"The inspections will generally be conducted at the decentralized site, where trial records and source documents

are located, " she said. "The relevant responsible individuals, the investigator and the study personnel should be available on site or by phone to answer any questions that may arise. When necessary, we may also inspect other facilities, local clinics and pharmacies for example, where trial-related activities occurred."

Grandinetti said the investigator and the sponsor should also save and archive all relevant communications and other records that demonstrate their oversight of the study, including oversight of adverse events, protocol deviations, data collection and handling and the shipment and delivery of study drugs directly to the study patients. This information should be available to the FDA on request during inspection.