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02 May 2023 | **News**

Decentralized Clinical Trials Could Affect Validity Of Non-Inferiority Finding, US FDA Says

by Brenda Sandburg

Draft guidance notes that data obtained from a decentralized clinical trial may be less precise than that from a site-based trial, creating challenges in calculating a non-inferiority margin. FDA specifies what should be included in DCT data management, trial monitoring and safety monitoring plans.

The US Food and Drug Administration's long-awaited draft guidance on decentralized clinical trials points out one challenge in using this approach: calculating whether the investigational drug is noninferior to an active control treatment.

"The variability and precision of the data obtained in a DCT may differ from the data in a traditional site-based clinical trial. This would not affect the validity of a finding of superiority in a trial using such data (although it could reduce the effect size), but it could affect the validity of a finding of non-inferiority," the draft guidance states.

The *draft guidance*, "Decentralized Clinical Trials for Drugs, Biological Products, and Devices," says that remote assessments may differ from on-site assessments, particularly when trial participants are responsible for performing their own physiological tests, such as home spirometry. It notes that assessments performed by local healthcare providers as part of routine clinical practice may also be more variable and less precise than assessments conducted by dedicated trial personnel.

"In non-inferiority trials, when the effect size of an active control drug, for example, has only been determined in a traditional site-based clinical trial, it may not be reasonable to assume that the same effect size would be seen for the active control drug in a DCT," the guidance states. "This may present challenges in calculating a non-inferiority margin. FDA review divisions should be consulted when planning a non-inferiority trial in a DCT setting."

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The FDA issued the guidance document on 2 May, fulfilling a requirement of the Food and Drug Omnibus Reform Act (FDORA) that was enacted into law last year. The statute required the agency to issue the guidance by 29 December. The guidance has been in the works for several years. The Center for Drug Evaluation and Research included the document on its 2020 guidance agenda of new and revised draft guidances it planned to publish that calendar year. (Also see "*Decentralized Clinical Trials Among Topics Slated For CDER Guidance In 2020*" - Pink Sheet, 2 Feb, 2020.)

"The FDA has long considered the benefits of decentralized clinical trials," FDA Commissioner Robert Califf said in a press release on the guidance. "Advancements in digital health technologies and the COVID-19 pandemic – when in-person visits were limited or unavailable for many trial participants – have accelerated the broader adoption of these activities."

"As we seek to improve our evidence generation system, decentralized clinical trials may enhance convenience for trial participants, reduce the burden on caregivers, expand access to more diverse populations, improve trial efficiencies, and facilitate research on rare diseases and diseases affecting populations with limited mobility," he stated.

Although industry interest in DCTs has grown over the last three years, the adoption of DCT elements is still in the early stages. Stakeholders have said that DTC-specific guidance would help instill greater trust in data generated using DCT methodologies. (Also see "*Decentralized Clinical Trials 'No Longer A Leap Of Faith'*" - Pink Sheet, 13 Feb, 2023.)

Fully Decentralized Vs. Hybrid DCTs

The agency said the draft guidance builds on recommendations it issued in March 2020, referring to the guidance "Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency," which it updated several times. The guidance addressed such issues as minimizing risks to trial integrity and factors to consider when switching from in-person to remote collection of clinical outcome assessment data. (Also see "*Clinical Trial Sponsors Should Consider Changing Data Collection Amid COVID-19, US FDA Says*" - Pink Sheet, 18 Mar, 2020.) and (Also see "*Decentralized Trials Guidance May Reflect US FDA's Lessons Learned During COVID-19*" - Pink Sheet, 25 Jun, 2020.)

A decentralized clinical trial refers to a clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites. The guidance notes that in fully decentralized clinical trials, all activities take place outside traditional sites, such as at the homes of trial participants or in local health care facilities. In hybrid DCTs, some trial activities involve in-person visits by trial participants to traditional clinical sites and other activities are conducted at other locations.

The guidance says fully decentralized trials may be appropriate for investigational products that

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are simple to administer or use, have well-characterized safety profiles, and do not require complex medical assessments.

It says hybrid decentralized trials may be more appropriate in cases where the administration of an investigational product (IP) or a complex medical assessment needs to be performed at a clinical trial site and some follow-up assessments could be performed remotely through online patient-reported outcome measures, via telehealth or in-home visits, or by local health care providers.

The guidance notes that whether the trial can be conducted entirely using remote visits or using a hybrid trial design depends on the types of assessments and procedures needed to collect endpoints and monitor safety.

For inspectional purposes, the guidance says there should be a physical location where all clinical trial-related records for participants are accessible and where trial personnel can be interviewed.

The document notes that the draft guidance "Digital Health Technologies for Remote Data Acquisition in Clinical Investigations," issued in December 2021, provides recommendations for measuring clinical events and characteristics of interest using DHTs to acquire data remotely from trial participants. (Also see "*FDA Draft Guidance Paves Way For Collecting Clinical Study Data Via Digital Health Technologies*" - Medtech Insight, 22 Dec, 2021.)

A Guide To Decentralized Clinical Trials

By Mark Terry

11 Apr 2023
In Vivo looks at some of the benefits and challenges created by decentralized clinical trials, how technology is being applied, and how regulators and researchers are working to prove the efficiency and cost-effectiveness of DCT trials compared to traditional clinical trials.

Read the full article here

Plans For Managing Data, Monitoring Safety

The draft guidance specifies what sponsors should include in a data management plan, trial monitoring plan, and safety monitoring plan for DCTs.

To account for multiple sources of data management, the guidance says a data management plan should include data origin and data flow from all sources to the sponsor; the methods used for remote data acquisition from trial participants, trial personnel and contracted service providers; and a list of vendors for data collection, handling and management.

Sponsors should describe in the trial protocol how operational aspects of the DCT will be implemented, including the scheduled and unscheduled clinical trial visits, delivery of

investigational products to trial participants, and safety monitoring and management of adverse events.

The guidance says a trial monitoring plan should describe how monitoring will be implemented to assess protocol compliance and data quality and integrity. It should also specify the frequency with which trial records and source documents will be reviewed and note any unique aspects related to the DCT procedures.

The FDA says sponsors should implement a safety monitoring plan to ensure the safety and welfare of trial participants. The plan should ensure that adverse events are appropriately captured and adequately addressed. It also should describe how participants are expected to respond to and report adverse events, including where to seek medical assistance locally, and describe the type of information to be collected by a digital health technology and how the information will be used and monitored.

'Decentralized Clinical Trials 2.0' On The Horizon

By Vibha Sharma

06 Feb 2023

The remarkable shift towards decentralized clinical trials in the last three years is a testament to how this patient-centric approach of doing research has the potential to solve multiple issues such as time, cost and low participation rates. In this first segment of a two-part article, the *Pink Sheet*looks at how innovation in this sector has just begun and...

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"If significant safety risks emerge because of the remote administration of an IP, sponsors must discontinue remote administration or use; notify FDA, the IRB, and all investigators who have participated in the trial; and determine if the trial should continue," the guidance states.

Delegation Of Trial Activities

The guidance also provides advice on investigator delegation of trial-related activities to local health care providers. It says local HCPs can perform procedures that require in-person interactions with trial participants, such as physical examinations.

"A critical consideration in a DTC when delegating trial-related activities to local HCPs is the potential for variability in the approach across different practices (e.g., documenting vital signs, physical examinations, and evaluation of adverse events)," the guidance says. "Quality control measures should be in place to help reduce variability, including regular review by investigators of participant data entered by local HCPs, to assess consistency and completeness of the required procedures."

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Regarding informed consent, the guidance says institutional review board oversight is required to ensure the process is adequate and appropriate. The agency recommends used of a central IRB in DCTs for review of the protocol, informed consent documents and other trial-related information.

Packaging And Shipping, Software Training

The FDA says DCTs generally may allow for the direct distribution of investigational products to trial participants at their locations. The protocol should describe how the physical integrity and stability of the product will be maintained during shipment, and a central distribution service could be used to ship the product.

In addition, the protocol should describe how investigators will track and document that trial participants receive the products and describe procedures for returning or disposing unused products and how this will be documented.

The guidance advises sponsors that they must comply with relevant local laws, regulations and licensing requirements governing medical practice and investigational product administration when conducting a DCT. It also says sponsors and investigators must comply with applicable federal, state and international laws and regulations that address shipping investigational products in their respective jurisdictions.

Finally, the guidance notes factors sponsors should consider regarding software used in a DCT. These include managing electronic informed consent, capturing and storing reports from remote trial personnel and local HCPs and clinical laboratories, and tracking investigational products that are shipped directly to trial participants. The agency says all parties using software to support the conduct of DCTs should receive training.

Comments on the draft guidance are due in 90 days. The docket number is FDA-2022-D-2870.