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ACDM Regulatory Considerations DMEG: Points to consider from the FDA guidance on Conducting Clinical Trials with Decentralized Elements

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Points to consider from the FDA guidance on Conducting Clinical Trials with Decentralized Elements

In September 2024 the FDA issued the final version of Conducting Clinical Trials with Decentralized Elements Guidance for Industry, Investigators and Other Interested Parties. The ACDM Regulatory Considerations DMEG reviewed the FDA guidance and identified items that have impact on data managers. This article summarizes those items and considerations for addressing them.

The FDA guidance joins prior publications from EMA and MHRA on expectations for decentralized trial methods that provide additional context for global implementation of decentralized trials. All three publications share a focus on defining roles and responsibilities, ensuring sponsors should engage patients and patient advocates and the importance of utilizing risk-based approaches in designing and managing decentralized systems. Furthermore, all three publications emphasize that trials utilizing decentralized methods must comply with existing GCP and regulations for conducting traditional clinical trials.

The EMA Recommendation paper on decentralised elements in clinical trials was published as part of the Accelerate Clinical Trials in the European Union (ACT EU). The EMA document is not a guideline but does provide detailed recommendations for implementing decentralized approaches. The document also contains an Appendix containing responses from member states (including the legislation reference) to questions related to conduct.

The MHRA Decentralised trial methods position statement is available as a webpage. While the MHRA webpage is not as detailed as the FDA guidance or the EMA recommendation paper, it does outline the MHRA expectations for sponsors utilizing decentralized methods. The webpage also provides links to related resources including the ACRO decentralized toolkit as well as the UK National Institute for Health Care and Research (NIHR) preliminary guidance on Remote Methods of Trial Delivery.

Highlights from the FDA Guidance on Conducting Clinical Trials with Decentralized Elements

The guidance discusses recommendations for implementing DCTs including design and conduct, remote trial visits, use of digital health technologies, roles and responsibilities of the sponsor and investigator, FDA oversight, Informed Consent, managing investigational products, safety monitoring and use of electronic systems. In this article the ACDM regulatory considerations DME focuses on the data management related issues noted in the FDA guidance.

The FDA defines a decentralized clinical trial (DCT) as one that "includes decentralized elements where trial-related activities occur at locations other than traditional clinical trial sites". FDA also reminds us that regulatory requirements are the same for DCT and non-DCT trials. Many DCT utilize digital health technologies (DHT) to support data collection. FDA defines digital health technologies (DHT) as "systems that use computing platforms, connectivity, software, and/or sensors, for healthcare and related uses." FDA also notes that additional relevant guidance on use of Digital Health Technology (DHT) is provided in the Dec 2023 FDA guidance on Digital Health Technologies for Remote Data Acquisition in Clinical Investigators.

Points to consider from the FDA guidance on Conducting Clinical Trials with Decentralized Elements

As with all clinical trials, it is necessary to implement Quality by Design (QbD) and Quality Risk Management (QRM) when designing and implementing DCT. Given the inherent complexities and risks related to the use of DHTs and decentralized methods, much of the guidance focuses on **study startup** and **trial design** considerations.

FDA recommends careful consideration of how trial design and use of DCT might introduce variability or bias. Data managers should utilize critical thinking in all aspects of DCT selection and implementation to assess the potential of bias and its impact on subject welfare and data integrity. The guidance provides several examples of how DCT selection and use could introduce bias.

For example, the trial design should limit variability in the data collected. This can be accomplished by providing clear instructions on how to collect data using DCT software. DMEG notes the following: data managers should provide support to the team in developing or reviewing the system training for trial personnel and participants to limit variability.

FDA also cautions that teams should also consider how use of DCT by sites, local HCPs and participants might introduce bias. For example, allowing participants to choose whether an assessment is conducted on site or remotely may result in bias. To avoid bias the protocol should specify which visits and assessments will be remote and which visits, if any can, be left to the participants' choice as to whether they are conducted on site or remotely. FDA emphasizes that trial design discussions should emphasize privacy during remote visits. FDA also addresses the role of local Health Care Providers (HCP) who may utilize the DCT systems and notes that while that HCPs may collect trial data they will not be considered Sub-Investigators. DMEG notes the following: As part of system setup and training careful consideration should be given to defining roles and rights for trial personnel including HCPs to ensure privacy and data integrity.

If the trial design includes Telehealth technology, i.e. the delivery of healthcare services using communications technologies, like video or online platforms, and the Telehealth technology is used to conduct visits this must be documented in the study records along with the date of the visit and the name of the person who conducted the visit. DMEG notes the following: that while data managers are not responsible for site study records, this requirement should be discussed with the team to ensure it is addressed in site training and monitoring.

The FDA also addresses expectations for selection and use of DCT and DHTs. Sponsors must ensure that they comply with both FDA regulations for use of DCT as well as applicable local regulatory requirements and laws. For example, systems used to produce or process trial records must be 21 CFR part 11 compliant and generally ensure data reliability, security, privacy and confidentiality.

In Section J Electronic Systems used when conducting DCTs FDA provides examples of systems that may be used to conduct DCTs including but not limited to electronic informed consent, eCRFs and communication tools.

Points to consider from the FDA guidance on Conducting Clinical Trials with Decentralized Elements

FDA states that sponsors must evaluate these electronic systems and DHTs to ensure they are available and suitable for use by all participants. The selection of DHT, including the option for participants to use their own devices, should never result in excluding potential participants from the trial. DMEG notes the following: As part of trial design and system selection, data managers should provide guidance to the team in ensuring selected systems will not exclude potential participants.

Because there are likely multiple sources of data collection in DCTs, the FDA notes the importance of documenting details of data flow in the data management plan (or other trial related plans). DMEG notes the following: As part of trial and system design data managers should provide input into or drive the development of the data collection strategy and assist the study team in designing the workflow and assessing operational and data integrity risks.

These plans should document:

- The data origin and flow from sources to the sponsor
- Methods and technologies used for remote data acquisition
- A list identifying service provides involved in data collection, handling and management

In addition, FDA notes that the trial protocol should describe the operational aspects of DCT implementation including:

- Scheduled and unscheduled trial visits
- Activities performed by trial personnel versus those that may be performed by local health care providers (HCP)
- Transmission of reports on activities performed at different locations
- Delivery of IP to trial participants
- Safety monitoring and management of adverse events

The guidance also discusses considerations for **study conduct** or **implementation** including traceability, ALCOA compliance, training, and centralized monitoring. The guidance reminds us DCTs must comply with requirements for ALCOA and expectations for traceability. As an example, when using DHT or DCT approaches, study records should capture the visit type, visit location, date of the visit, and data originator. DMEG notes the following: for e-source or direct digital capture, data managers should ensure this information is recorded.

In line with regulatory requirements for DCT and traditional trials, all systems users must be trained to utilize the system. This includes local HCPs who may enter data directly into an eCRF or send electronic documents to the investigator for entry into the eCRF. The guidance notes that Investigators are required to review data entered by other trial personnel, including local HPCs, and follow up on data that are missing or appear discrepant or concerning. In addition, the investigator must review reports from local HCPs of abnormal signs or symptoms and follow up as appropriate.

DMEG notes the following: data managers should ensure the CRF and system design supports Investigator review for forms entered by the local HCP.

Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations Questions and Answers Guidance for Industry

TFDA notes that real-time video and audio interactions between trial personnel and participants are not considered electronic records and are not subject to 21 CFR part 11. But the data obtained during those visits must be documented in the study record. If the documentation is electronic, then the systems used to capture and store the documents are subject to 21 CFR part 11.

Regarding study monitoring, the FDA notes that sponsors should take a risk-based approach to monitoring. Centralized monitoring can be utilized to identify and address missing or inconsistent data, data outliers, and potential protocol deviations.

While the guidance does not contain specific sections related to **study close or archival**, the FDA reminds us that DHT and DCT systems should comply with 21 CFR part 11 requirements which include retention, inspections, and audits. The Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations Q and A contains further details on FDA expectations for these areas.

The graph below provides of examples of key considerations for each study phase.

Key Considerations by Study Phase (Setup, Conduct, Closure)

Setup

- Consider that all sponsor responsibilities in a traditional trial are applicable in a DCT (Section D)
- During trial design, consider measures to limit variability in the data collected. This can be accomplishes by providing clear instructions on how to collect data using DCT software (Section A)
- Describe operational aspects of DCT implementation in the protocol (Section C)
- Document data flow, methods or technologies and services used to collect data from all data sources in the DMP (Section C)
- Design data acquisition tools to capture the visit type, visit location, date of the visit, and data originator (Section C)
- Systems used to produce or process trial records are subject to 21 Part 11 and must ensure data reliability, security, privacy and confidentiality (Section J)

Conduct

- Ensure privacy during remote visits (Section B)
- Consider different roles and responsibilities of HCPs and site team (Section B)
- Make sure relevant information is captured in study records when telehealth technology is used to conduct visits, e.g. visit type, visit location, date of the visit and data originator (Sections B & C)
- Consider decentralised monitoring approach when appropriate (Section D)
- Keep record of remote staff or local HCPs submitting data directly into the eCRF. Sponsor should maintain a list of authorized originators (Section J)

Closure

- Consider different roles and responsibilities of HCPs and site team (Section B)
- Consider that all sponsor responsibilities in a traditional trial are applicable in a DCT, thus data retention planning, system decommissioning, etc. should be arrange accordingly (Section D)

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