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WHITEPAPER

TAKEAWAYS & PERSPECTIVES: FDA DRAFT GUIDANCE ON DCTs

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In May 2023, the U.S. Food and Drug Administration (FDA) released draft guidance entitled "Decentralized Clinical Trials for Drugs, Biological Products, and Devices" [1]. This is a welcome insight into the agency's thinking related to the use of decentralized elements and fully decentralized trials. It is also especially pertinent in the context of the recent recommendation paper on decentralized elements by European Medicines Agency (EMA) [2]. In their draft guidance, out for public comment for 90 days, FDA define a decentralized clinical trial (DCT) as "a clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites", and use the term hybrid DCT to refer to a trial using a combination of in-person site visits alongside activities conducted at other locations, such as at participants' homes.

A number of themes are represented, and we summarize these below, with additional reference to the EMA recommendations.

THEME 01

APPROACHES WE COMMONLY ASSOCIATE WITH DECENTRALIZED ELEMENTS ARE REFERENCED POSITIVELY

FDA identify a number of approaches that could be considered when designing a trial with decentralized elements. These include:

- Remote consenting
- Telemedicine (video visits) and Digital health technologies (DHTs, e.g., electronic patient-reported outcomes (ePRO) solutions and wearables/sensor devices) used by the patient at home
- Home nurse visits and the use of local healthcare services
- Direct-to-patient medication provision

Remote consent

FDA indicate that remote consent may be considered as part of a DCT, subject to the process being deemed adequate and appropriate by an Institutional Review Board (IRB). Within this process, participants should always have the ability to contact trial personnel to seek answers to questions about the trial, and this could be achieved by a remote visit, such as using a video visit.

Telehealth (video visits)

FDA identify that video visits can be considered if the assessments and procedures to be conducted support this approach. In these cases, it will be important that investigators confirm the patient's identity during the video visit, and that visits are documented.

Digital health technologies (DHTs)

DHTs are well covered by FDA's other draft guidance specifically on this topic [3], but the agency reiterates in this draft guidance the importance of ensuring that trial participation is not restricted by DHT ownership. In the case of bring-your-own-device (BYOD) approaches to ePRO or sensors/wearables, participants without a suitable device, or unwilling to use their own, should be provided with a provisioned solution.

Home visits and local healthcare providers

Much of the draft guidance's focus on the use of home nurses and local healthcare professionals (HCPs) relates to the delegation of activities and ensuring investigator oversight and responsibility, which we discuss in theme 2, below.



Direct-to-patient (DtP) medication provision

FDA identify medications considered suitable and unsuitable for DtP methods. Unsuitable medications may include those with complex administration procedures, a high-risk safety profile, or are in early development in which the safety profile is less well understood. They suggest that drugs best suited to home delivery include those with long shelf lives and good stability profiles, and drugs not requiring specialized handling, shipping, and storage conditions. In terms of shelf life, most randomization and trial supply management (RTSM) systems (including that provided by Signant Health) are able to ensure allocation of medication with sufficient shelf life to mitigate this. In the event of DtP provision, RTSM systems may accommodate additional time buffers within "do not ship" and "do not allocate" decision rules to allow for longer shipment windows due to (for example) failure to deliver due to the patient not being at home.

When using DtP for some or all of the scheduled and unscheduled medication dispensing events, the protocol should describe how the physical integrity and stability of the investigational product (IP) will be maintained during shipment to trial participants. Further, the investigator must maintain their prescribing authority such that the investigator themselves, or delegated trial personnel, must control the release of the investigational product by the distributor, monitor receipt and use by the patient, and monitor the return or disposal of any unused medication. The protocol should describe how investigators will track and document that trial participants receive their medication. RTSM systems with specialist DtP functionality, like Signant's, enable these requirements, enhanced by integration with specialist last-mile courier providers.



THEME 02

CONSIDERATION OF INVESTIGATOR OVERSIGHT AND RESPONSIBILITIES

FDA identify that trials with decentralized elements may involve assessments conducted by local HCPs or other trial personnel, and state that in all cases, while sponsors are responsible for the proper coordination of outsourced decentralized activities, investigators are responsible for the oversight of individuals delegated to perform trial-related activities. This is fundamental to maintaining good clinical practice (GCP) principles, and in line with the statements made by EMA in their recommendations paper[2]. EMA, in fact, go into more detail, and state that decentralized elements should be considered an extension of the clinical site, and that investigators should determine the adequacy of contracted third parties where activities are delegated from investigator responsibilities. To satisfy this EMA requirement, the contract between the sponsor and investigator should clearly outline these delegated tasks, and the investigator should be furnished with sufficient information to be able to appraise the suitability of a delegated party's qualification and experience.

FDA identify that certain technologies may facilitate the oversight of remote activities conducted at home, such as a home nurse procedure. Remote monitoring technology, such as the use of video glasses connected to Signant's telemedicine solution, may facilitate this where close oversight and active instruction is required.

Investigators are responsible for the patient case record, and when some of this data is collected by a local HCP, it might be entered directly into the clinical trial technology solution (e.g., EDC) by the HCP to enable investigator access and review. In cases where data collection by other means is necessary, measures should be taken to ensure secure upload of forms and documents for direct transfer to the investigator. The investigator or site personnel should then input the data into the appropriate technology solution. While not emphasized, the term "direct transfer" is key – locally collected data should not go first to a sponsor system, but it must always be assured that the investigator has access to, and control of, the original source record.

It will be important to ensure that remotely collected data are fully included in the investigational oversight of each patient. The FDA draft guidance requires regular review of data collected by local HCPs. EMA recommend that the review frequency of each data source by the investigator should be based on the relevance of the data to the safety and well-being of the trial participant, and the relevance of the data for the assessment of treatment efficacy [2]. Further, FDA state that ensuring adequate patient supervision at all times is vital, so investigators in decentralized trials should not recruit more patients than can be managed and overseen effectively.

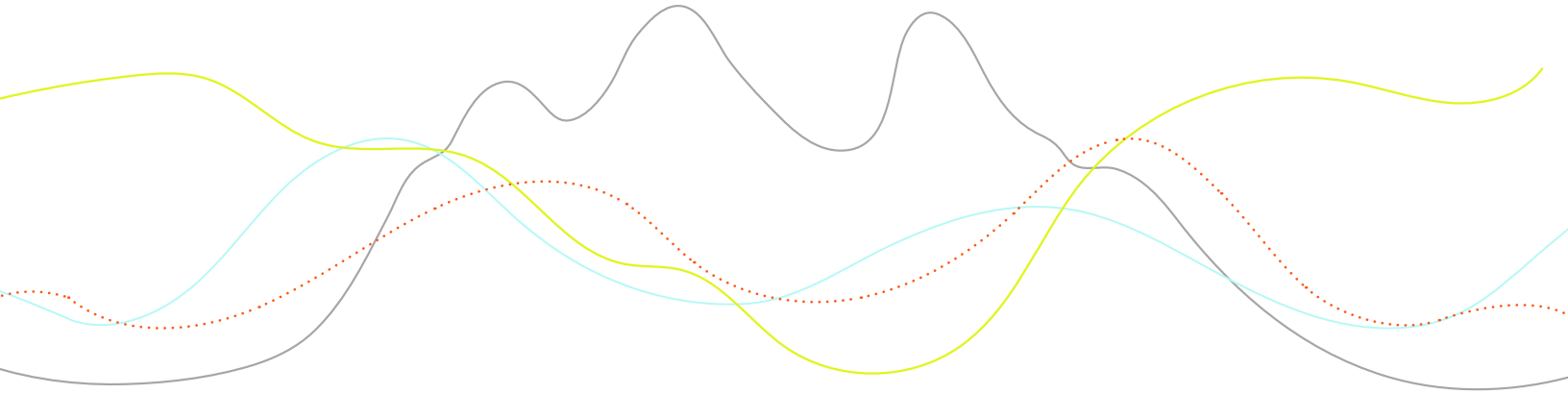
As part of their responsibilities, the investigator should maintain a task log of local HCPs who perform delegated trial-related activities.

THEME 03

PRESERVING DATA PRECISION AND VARIABILITY

FDA state that remote assessments conducted by the patient themselves or by a local HCP may be subject to greater variability than those performed by dedicated site personnel. Although not stated, this may also be true of trials designed to enable more than one setting for assessments across their period of study. The agency requires that 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. We discussed the oversight of HCPs in the theme above, but the wider quality control requirements are important, and why at Signant we leverage clinical and data science experts to conduct ongoing data review to identify and mitigate emerging data quality concerns. For example, when conducting patient assessments both remotely and on-site for different visits, risk measures might include any increase in variability in data collected remotely and any drift in data consistency or precision between the assessment methods and settings.

Overall, while the guidance does not go into great detail, it does provide valuable perspective on the agency's views regarding the use of decentralized elements in clinical trials. Together with the recent EMA recommendations paper, this provides good endorsement of our current direction of thoughtful application of decentralized elements to optimize trials and trial participation.



REFERENCES

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