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Considerations For Using Established Versus Novel Endpoints In Decentralized Trials

by Vibha Sharma

UK and US regulators explained why some established clinical endpoints are not suitable for use in decentralized trials, and discussed principles to guide the development of novel digital endpoints.

A key consideration for sponsors planning to conduct decentralized clinical trials (DCTs) is the selection of appropriate clinical endpoints that are meaningful for regulators, health professionals and patients.

As DCTs require that some or all study-related activities are conducted at a location remote from the trial investigator, the selection of appropriate endpoints is made more complex due to the different ways in which data can be gathered – eg through the use of electronically-captured outcomes versus medical measurements in a laboratory, or the need for at-home visits by nurses.

Sponsors can either use established clinical endpoints or develop novel ones, according to Khadija Rantell of the UK Medicines and Healthcare products Regulatory Agency. But for any endpoint to be valid, it should "capture the outcome of interest accurately" and "consistently, with repeated measurements," and with "minimum error or uncertainty," she said.

Rantell, senior statistical assessor at the MHRA, was speaking at this month's virtual 2022 Good Clinical Practice (GCP) symposium, which was organized by the MHRA in partnership with regulators from the US and Canada.

'A Lot To Consider' For Sponsors Planning Decentralized Trials

By Vibha Sharma

She said that while an established endpoint represented a "reliable measure of clinical benefits

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in the target population based on therapeutic progress and knowledge in the field," sponsors must consider several factors when it comes to their use in DCTs.

These factors will depend on the type of endpoint itself, which may be laboratory-based, investigator-assessed or patient-reported, said Rantell. The "type of assessment and therapeutic area" will also have an impact.

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A senior MHRA official tells sponsors not to get "put off" by the many factors they need to examine when deciding on the suitability of decentralized trials, and instead seek early advice from regulators.

Read the full article here

> ***'Consider undertaking upfront comparability studies to better understand why on-site and remote assessment of an endpoint may be different — Khadija Rantell, MHRA***

As with traditional trials, Rantell said the methods used for measuring subjective and objective endpoints in a DCT "should be validated and meet appropriate standards for accuracy, precision, reproducibility, reliability and responsiveness."

As a general principle, "it is important to maximize [the] quality of the data, minimize variability and ensure generalizability of the results in a trial by design" for which "pre-specification and pre-planning" are key, she added.

Rantell suggested that sponsors should consider undertaking "upfront comparability studies to better understand why on-site and remote assessment [of an endpoint] may be different." Dissimilarities may arise due to factors such as ascertainment bias, missing data, confounding variables, the lack of training or inadequate operating procedures.

There should be clarity on which data would support remote safety monitoring of the trial, and which data are for study endpoint analysis, she added. The technologies used for capturing data "must be demonstrated, validated and comply with the relevant standard for accuracy, precision, reproducibility, reliability and responsiveness" Rantell said.

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'There are scenarios where an established endpoint accepted in a traditional trial would not be accepted in a decentralized trial' — Khadija Rantell, MHRA

Irrespective of these considerations, the MHRA official said: "There are scenarios where an established endpoint accepted in a traditional trial would not be accepted in a decentralized trial." These include:

- The six-minute walk test (6MWT) – This in-clinic measurement "cannot be easily administered in the real-world for several practical reasons," observed Rantell. The test involves the trial participant having to walk at a comfortable pace between two cones, placed 30 metres apart on a flat surface and in a straight line. It is supervised by site personnel to avoid the possibility of the patient falling over, prevent over-exertion and to motivate the patient to continue walking for the full six minutes. "This type of supervision provided by a caregiver may not be readily available at home," the MHRA official noted.

- The use of digital photography to assess skin lesions, for example, in psoriasis — Commonly used endpoints in psoriasis trials are the Psoriasis Area and Severity Index, Body Surface Area, and the Physician's Global Assessment of Severity. More than one endpoint is often required to assess treatment efficacy. "A reasonable consistency of response is expected with respect to the employed measures" and this is usually achieved by training investigators in using all instruments of measure in which the image quality "plays a significant role in helping the clinician in their assessment of the lesion," noted Rantell. As the quality of digital photos in a DCT may vary, "it may be difficult to ensure the reliability and consistency of the assessment," she said. Inconsistencies may also arise if the endpoints used are assessed by different doctors for the same trial participants.

"Of course, there are situations where established endpoints in traditional trials may be used in decentralized trials," but "their appropriateness will be judged on a case-by-case basis," Rantell noted.

Novel Endpoints

DCTs often involve the use of digital health technologies, making it possible to capture endpoint data directly from patients.

To develop novel digital endpoints, sponsors should follow the same guiding principles as for developing novel endpoints captured by other means, said Phillip Kronstein of the US Food and

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Drug Administration, who was also speaking at the symposium.

They should, for example, first determine whether the novel endpoint is a "clinically meaningful reflection of how a participant feels, functions or survives" and whether it can be adequately captured using digital tools, said Kronstein, who is lead medical officer at the FDA's Office of Scientific Investigations.

Other factors to consider for developing digital novel endpoints include the following:

- Whether the novel endpoint is a sufficiently reliable measure of disease severity or health status (eg, mild, moderate or severe) to allow assessment of disease modification or progression.

- How the novel endpoint relates to previously established endpoints of effectiveness that have been used to support a marketing authorization for a similar indication. In the absence of related endpoints, "evidence from other sources of information, such as literature or input from stakeholders and experts" can be used to support the use of the novel endpoint, Kronstein said.

- If a medical product has been approved based on evidence from a study using an established endpoint for the disease or condition of interest, "it may be useful to determine whether the effect of that existing medical product can be detected using the novel endpoint," the FDA official noted. In such a case, the existing medical product will act as a "positive control."

- Consider the need for usability studies to assess whether the intended population in a DCT would be able to use the digital health technologies as directed in the trial protocol. For example, elderly subjects might not be able to use electronic devices for recording patient-reported outcomes.

- Ensuring that the digital health technology is verified and validated for its intended purpose. In cases where the digital technology only replicates existing measurements for the same clinical endpoint, (eg, weight measurements at home versus in the clinic), the "FDA generally would not expect sponsors to provide a new justification for the endpoint," Kronstein said.

The FDA official said that sponsors should discuss their plans for novel digital endpoints with the relevant review divisions at the agency. "The earlier the engagement… the better," ideally as early as the pre-investigational new drug application stage, he said.

Last year, the FDA also issued draft guidance on how sponsors can use digital health technologies to acquire data remotely from participants in clinical investigations of medical

products. (Also see "*FDA Draft Guidance Paves Way For Collecting Clinical Study Data Via Digital Health Technologies*" - Medtech Insight, 22 Dec, 2021.)