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EU Regulators Told To 'Normalize' Decentralized Clinical Trials

by Vibha Sharma

EU drug regulators have received some candid responses from trial sponsors and other stakeholders on the aspects that should be urgently addressed in the next iteration of their guidance on decentralized clinical trials.

EU regulators looking for feedback on what stakeholders made of their recommendation paper on decentralized clinical trials, which was issued nearly a year ago, have been flooded with suggestions for improvement, starting with keeping an open mind and not holding DCTs to a higher degree of scrutiny than conventional site-based trials.

Regulators were told to refrain from "making assumptions" on what patients or principal investigators might prefer in a trial, and to provide guidance on how to involve local health care providers in DCTs if they are not part of the study team.

On top of that, stakeholders wanted the regulators to highlight areas of uncertainty and national differences on the acceptability of decentralized elements in EU member states, address issues around data variability and integrity, and clarify the pathway to support the faster approval of digital endpoints.

These and other suggestions were made by trial sponsors from academia and the pharmaceutical industry, as well as statisticians' and patients' representatives, at a multi-stakeholder workshop organized by the European Medicines Agency on 23 November. The workshop focused on ways to support the uptake of novel clinical trial methodologies, including DCTs, which allow some or all trial activities to be conducted in participants' homes and local settings rather than at investigative sites. (Also see "*EU Aims To Foster Innovation Through Streamlined Uptake Of Clinical Trial Methodologies*" - Pink Sheet, 28 Nov, 2023.)

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The way the EU DCT recommendation paper is currently framed conveys the message that site-based trials are the gold standard and that "decentralizing brings extra risks," or that "you have to prove that it's just as good," noted Mira Zuidgeest, the principal investigator of the much-hyped RADIAL trial that is simultaneously testing patient experiences in fully remote, hybrid and site-based conventional arms in five EU countries and the UK. (Also see "*Decentralized Trial Approaches: How Do They Match Up To Conventional Studies?*" - Pink Sheet, 11 Nov, 2022.)

Regulators should look at "whether we can, for lack of a better word, normalize DCT approaches," said Zuidgeest, who is an associate professor of clinical trial innovation at the University Medical Center (UMC) Utrecht, the Netherlands. The aim should not be to "create dichotomy" because a DCT is just an operational model that comes with its own challenges and advantages compared with a site-based model, she added.

Zuidgeest noted that sponsors should be able to add decentralized elements to a trial, which may be better or worse than site-based activities depending on what the trial wants to achieve. "We [should] always try to talk about decentralized trial approaches rather than decentralized trials," she suggested. (Also see "*Experts Want To Drop Confusing Terminology For Decentralized Clinical Trials*" - Pink Sheet, 23 Feb, 2023.)

Amgen's Alison Bond agreed that "rather than talking about decentralized clinical trials or traditional trials," the long-term vision should be to ensure that "decentralized elements become part of the clinical trial toolbox along with pragmatic elements" so that sponsors can choose the most appropriate methods, tools and technologies to answer the scientific question and meet patient needs.

Keeping An 'Open Mind'

Zuidgeest advocated against placing additional obligations on sponsors of DCTs as these are subject to the same regulations as conventional trials.

The DCT recommendation paper, she noted, requires sponsors to describe in the study protocol a risk-benefit assessment of the critical decentralized elements they intend to use in a trial, along with a description of risk mitigation measures to be deployed. "Those things are usually not required for a protocol," she noted.

When seeking approval for the RADIAL trial, Zuidgeest said: "We had many requests [from EU regulators] whether we could specifically explain a procedure in a protocol." The queries were about aspects that are usually never put in a protocol, "but are part of working instructions," she noted.

The paper also talks about "additional obligation of oversight for investigators and sponsors" because in DCTs patients are at home. However, Zuidgeest noted that in conventional clinical

trials too, patients are mostly at home and visit the site every now and then.

It is these perceptions that need addressing, she said. “I understand we're working on something new so maybe we're thinking things through in a way that we don't do for the conventional setup anymore,” she noted.

Just as some decentralized elements, like e-diaries, have already become common practice, Zuidgeest said in the future it would be common to have more and more trial elements decentralized and not on site because these “make sense from a patient perspective,” are “easy to implement” and “don’t come with great risks.” However, this can only work “if we have an open mind,” she declared.

On concerns around monitoring patients at home, Zuidgeest said there were opportunities for learning from projects being trialled in hospital settings where a lot of care is moving to the patient’s home. “We have over 15 projects in our hospital” to try and get patients “either to stay at home or go back home earlier” so that they can be monitored there, she noted.

> *‘Sometimes it was felt indeed as if things were scrutinized to a higher degree’ – Mira Zuidgeest, principal investigator, RADIAL trial*

Zuidgeest’s general impression was that when undertaking the RADIAL trial, her team had to “defend very often why we were trying to do certain things in a certain way” and “sometimes it was felt indeed as if things were scrutinized to a higher degree.”

In response to Zuidgeest’s observations, Monique Al of the EU Clinical Trials Coordination Group (CTCG) said the aim of the recommendation paper was to provide a risk-based, patient-centerd approach for DCTs, but “I get the feeling that in certain aspects we maybe failed a little bit.”

Tiina Holmberg of the Finnish Medicines Agency (Fimea) said that in the DCT recommendation paper regulators were not saying that the “old way is perfect” and that “if you're trying to do anything new, you need to do something additional.” Many points in the paper were also relevant for traditional trials as the same considerations apply, said Holmberg, who is a good clinical practice inspector at Fimea.

The paper was issued with the aim of giving some regulatory advice on DCTs “because we kept being asked ‘Do you accept decentralized trials?’” explained Holmberg. It was a question that

became “impossible to answer” and when drawing up the paper, regulators focused on the issues that they thought stakeholders wanted advice on, she said, adding that the stakeholder feedback would help regulators to “have another look and see whether we can improve the guidance.”

Do Not Presume What Patients Prefer

The DCT recommendation paper requires sponsors to have procedures in place to accommodate situations where patients might wish to give live informed consent or want to be onsite to see the trial investigator in person. Also, it recommends providing alternatives if patients are not willing to use their own device (eg, smartphones, tablets) to capture trial data.

These requirements convey that it is mandatory to have a site-based activity as a backup in DCTs, said Zuidgeest. However, if not required from a safety or oversight perspective, then such requirements should not be mandated because there is no at-home backup for conventional trials either, she argued.

Zuidgeest suggested that regulators should focus on “what's required from a regulatory perspective” and leave out aspects relating to patient preferences, which can differ greatly. The topic of patient preferences, she said, should be dealt by trial design teams, who “should include patient representatives in the correct manner to determine what the actual preferences are and then to see what can be accommodated in a specific trial.”

Christine Dehn of the German Heart Foundation pointed to concerns in the recommendation paper that DCTs may result in the exclusion of certain patients, such as those who are not digitally literate or have a poor internet connection. Dehn does not believe this is such a big issue as most people, including the elderly, have smartphones these days.

Other areas in the DCT recommendation paper identified by stakeholders that need addressing include:

- Highlighting areas of uncertainty and national differences, such as the lack of harmonization among member states on the acceptability of electronic signatures. During the RADIAL trial, Zuidgeest’s team also identified the need for additional approvals, such as customs requirements for shipping to the UK the investigational medicinal products (IMP) that were packaged in the EU. She explained that as per UK post-Brexit customs requirements, the IMP kits needed an “importer of record,” an entity responsible for ensuring the imported products comply with local laws and regulations, but as the kit had various components, no manufacturer wanted to take responsibility for the elements that were not from them, nor was it possible for the trial sponsor to take on this role. The issue was finally resolved with the UK site taking on that role for the IMP kits. (Also see "*EU Picks Up The Pace On Home Delivery Of Study Drugs*" - Pink Sheet, 14 Sep, 2023.)

- Providing guidance on how to involve local health care providers in DCT-related procedures without making them a part of the study team. “We have had a lot of discussions in the Netherlands with primary care physicians” who want to be involved in a trial, but do not have the time to undergo trial-related training, said Zuidgeest.

- Measuring differences between clinic and remote assessments, and how to ensure data integrity and quality. (Also see "*EU Regulators Urged To Address Impact Of Decentralized Trials On Data Quality & Integrity*" - Pink Sheet, 12 Jan, 2024.)

- Supporting the use of digital health technologies (DHT), outlining how to get DHT-derived endpoints accepted faster, and explaining related key validation criteria. (Also see "*EU Pharma Wants Regulators’ Help To Simplify Digital Endpoints Landscape*" - Pink Sheet, 30 Nov, 2023.)

- Developing ways to share operational learnings with the broader community.