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# Decentralized Trial Approaches: How Do They Match Up To Conventional Studies?

by Vibha Sharma

Mira Zuidgeest is the principal investigator of a key EU study that proposes to compare fully remote, hybrid and conventional clinical trial approaches. She talks to the *Pink Sheet* about how the study might help understand "where we're heading with decentralized clinical trials."

A proposed EU clinical trial of around 600 people living with diabetes who will be treated in the study in one of three different locations – 300 at their homes, 150 in a hybrid setup (part home, part trial site) and 150 at a trial site – is being closely watched.

The study, called RADIAL (Remote And Decentralised Innovative Approaches to clinical triaLs), is part of the Trials@Home project that is being funded under the Innovative Medicines Initiative - a public private partnership between the EU and the European pharmaceutical industry body EFPIA.

It is expected to provide key insights on whether decentralized clinical trials (DCTs), which are performed in or near a participant's home, are as good as or even better at delivering research outcomes compared with conventional trials, which are traditionally performed at clinical sites.

"Our trial is a bit different in the sense that it's a methodological trial," RADIAL's principal investigator, Mira Zuidgeest, said in an interview with the *Pink Sheet*.

In the trial, "we are not comparing two drugs with each other but looking at different operational approaches," explained Zuidgeest, who is an Associate Professor of clinical trial innovation at the University Medical Center (UMC) Utrecht, the Netherlands.

The trial will compare the performance of the three arms – fully remote, hybrid and conventional – against scientific and operational parameters including the quality of data generated and the

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management of patient safety, because “if you don't have these [criteria], then the trial won’t be approved,” said Zuidgeest.

More importantly, it will compare the three arms against other parameters, such as recruitment speed, the diversity of trial subjects, retention numbers, study cost involved, and the satisfaction levels of participants and investigators and site teams with the trial’s set up.

One of the biggest problems with trials at present is that participation is “often quite burdensome” and “difficult to fit in” with the daily lives of participants, Zuidgeest said.

RADIAL will help measure whether the convenience of participating in research from one’s own home or at nearby locations can improve enrolment rates. If the trial’s setup “is not interesting for participants and for sites” then “it may be scientifically sound, but your trial won't run,” she noted.

## Operational Move

Zuidgeest became interested in DCTs from her work on pragmatic trials, which involves developing trials in such a way that they can better answer questions in clinical practice.

DCTs, she believes, are a “really good operational way to bring trials to patients” while making sure that “the way we research an intervention” is “closer to real life.”

On hearing about the IMI’s call for the Trials@Home project in 2019, Zuidgeest and the head of her team Diederick Grobbee, professor of clinical epidemiology at UMC Utrecht, decided that they wanted to get involved. (Also see "*Remote Decentralized Clinical Trials Could Solve RCT Problems*" - Pink Sheet, 21 Nov, 2019.)

It piqued their interest because they had always been keen on understanding how trial methodologies and trial operations interact, “because you can't see them separately” and this was “such an interesting operational move within the clinical trial field,” Zuidgeest said.

The UMC Utrecht kicked off its part of the Trials@Home project by setting up an academic consortium, which was later merged with the industry consortium as is usual with IMI projects. Zuidgeest said it was nice to see that both the academic and industry partners had the same

vision. “The plans we had for the project were very much in line with what they wanted to do.”

For industry and academic trial sponsors, results from the RADIAL trial will help evaluate the feasibility of deploying decentralized elements in clinical trials, especially in the EU, where member state-specific requirements on the execution of DCTs have been repeatedly highlighted as a major hurdle by sponsors. (Also see "*Is It Tougher To Conduct Decentralized Trials In The EU? ‘Don’t Fall Prey To Negative Narrative’*" - Pink Sheet, 11 May, 2022.)

Zuidgeest acknowledged that while there was no EU-wide consensus on topics such as direct-to-patient shipment of investigational medicinal products and remote informed consent, there was a real push from the EU regulators to drive DCTs forward. (Also see "*EU Takes Focused Approach In Bid To Deliver Decentralized Clinical Trials Guide By Year End*" - Pink Sheet, 25 Oct, 2022.)

“It's good we're doing this [study] because with a methodological trial, we can test these aspects” and “figure out where the difficulties still are,” she said. And it is “better to do that in our [methodological] environment than when you want to do a clinical study for a new drug.”

## Fingers Crossed On Approval & Enrolment

The RADIAL trial is now at a critical juncture, having been submitted for review in March in five EU countries (Denmark, Germany, Italy, Poland and Spain) and in July in the UK. Denmark authorized the study on 2nd November, and Zuidgeest and her team are now waiting for news on its approval in the other countries, which is expected any time now.

While the RADIAL team held extensive early dialog with regulators and ethical review boards to accommodate their feedback prior to the trial’s submission, the team would breathe easy only when the study is approved in the remaining countries.

“I think as long as a project like ours is in the submission [phase], you have no idea” what regulators and ethics committees “might come back [with]... and see as flaws within the [trial] design,” Zuidgeest said. “We have thought through the design in so much detail, but a fresh pair of eyes can look at it differently,” she said, adding that she was currently focused on “anticipating what type of feedback we [might] get back from the review of the trial.”

If RADIAL gets accepted in all the six countries, participant recruitment can begin, and it can start producing results that can then be merged with insights from the other work packages of the Trials@Home project. This will help to deliver “good recommendations on where we're heading with decentralized clinical trials,” Zuidgeest said.

People living with diabetes were involved in developing the trial’s protocol and feedback from patient representatives regarding the proposed study has also been positive. But patient engagement will also be important during the recruitment phase. “Given that this is a

methodological study, I really hope that people living with diabetes... see the possible added benefits of decentralized clinical trials and would want to participate," she said.

Zuidgeest said the enrolment target of 600 patients was based on a "thorough feasibility analysis," but clarified that there was uncertainty on the pace of recruiting the 300 participants for the remote arm because it is a relatively new concept, for both the trial sites and the patients.

"It may be that enrolment to the fully remote arm proceeds much faster or slower than anticipated, and both situations have been accounted for," Zuidgeest said.

As for the enrolment target of 150 patients each for the hybrid and the conventional arms, Zuidgeest said: "We are pretty sure about the numbers" because of the available experience on this front.

The RADIAL team expects to have the first trial site activated in December. This would be followed by a six-month participant recruitment period, and another six months for following up on participants. The final trial results are expected in Q1-Q2 of 2024.

## Technology Aplenty

The study is targeted at people living with type 2 diabetes who have reached the stage of requiring basal insulin. The participants would be divided into groups A and B.

Those in group A would be recruited via traditional site-based methods and randomized 1:1 either to the conventional arm (and then followed via telephone and on-site visits) or the hybrid arm (followed via a mix of on-site visits, an at-home nurse visit and remote tools). Group B, the fully remote arm, would be recruited through an online platform and followed exclusively remotely, through telehealth visits and remote tools.

All participants would receive the same intervention – Sanofi's Toujeo (insulin glargine). For the remote follow-up of patients in the fully decentralized and hybrid arms, the RADIAL team will use existing technologies available on the market and will not be testing new wearable monitoring devices.

"You would be amazed" at how much technology is already available to support DCTs, remarked Zuidgeest. In RADIAL's case, she explained, the team will make use of technologies "that you would need for any decentralized trial" such as a DCT platform, a customized study app, video conferencing, etc.

On top of that, the trial will use a smart sensor developed by Biocorp that can automatically capture insulin injection data. The sensor is a cap that is placed on the insulin pen and registers the injected dose, Zuidgeest explained.

This dosing data will then be integrated with a digital medication adherence tool, called MEMS AS, which was developed by AARDEX Group. This will provide an optimal understanding of participant compliance during the course of the study. “There's already quite a lot [of tech involved] even if you're doing a decentralized trial without new technologies,” she noted.

On the use of technology in the conventional arm, Zuidgeest clarified that this would follow the current state of the art. It will involve site visits and phone calls, but also an electronic patient diary “because most trials use electronic patient diaries these days,” she said.

## The Site Perspective

While decentralized trials hold the potential to make research faster and more efficient, there have been instances of poorly designed DCTs putting undue pressure on staff at trial sites. (Also see "*Denmark Finds Sponsors ‘Overburdening’ Study Sites To Support Decentralized Trials*" - Pink Sheet, 27 May, 2022.)

This can happen when the site’s perspective is not taken into account from the start. “Now people are realizing how important” this problem can be,” said Zuidgeest. As the staff at trial sites have to work with the new digital and remote systems, “it's very important that they have confidence” in this new way of working and that “it doesn't add extra burden.”

Within RADIAL, this issue is being addressed in different ways. While “people with site experience” have helped with the trial’s design, there are plans to collect regular feedback from site staff regarding what they liked or disliked about RADIAL “so that we can learn from that,” she said.

Zuidgeest said her team had made a great effort to ensure that RADIAL does not end up being “a lot easier” than other DCTs because “then the learnings wouldn't count.” This means that RADIAL sites will have to work with more than one system to execute and monitor the trial. As in any trial, sites will be trained on these systems and the trial in general. The need for additional training and support for site staff for DCT approaches in general is also being explored.

## Hands Full

In addition to being the overall academic lead for the Trials@Home project, and the lead investigator of the RADIAL trial, Zuidgeest is working on other projects, for example on pragmatic trials and strengthening the “trial climate” at UMC Utrecht. As full-time researcher at the UMC Utrecht, she is also involved in teaching and supervising students and PhD candidates.

Zuidgeest is also a frequent face at DCT-related conferences and workshops, given the high level of interest in RADIAL and the other workstreams of the Trials@Home project. “There are already some very nice publications” from the Trials@Home consortium, eg on the mapping of the DCT regulatory landscape during the COVID-19 pandemic, and on ethical considerations surrounding

DCTs, she said.