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# Getting the most out of digital endpoints: case studies from Verge's CMO

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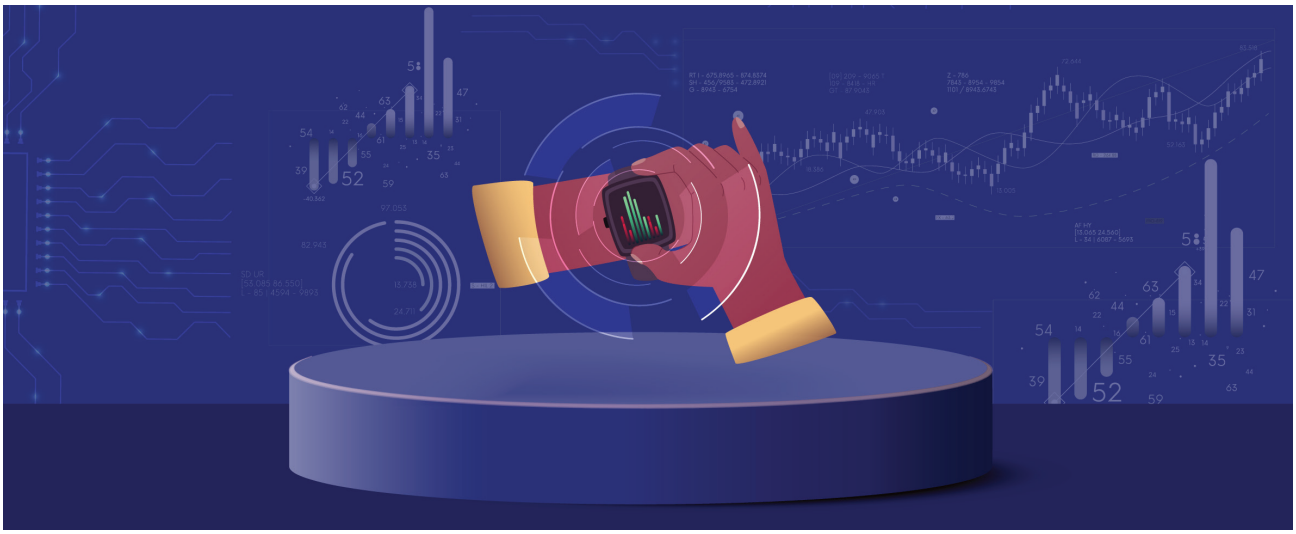

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With digital endpoints increasingly valued by biopharma, but not yet mainstream, Verge Genomics CMO Diego Cadavid's career provides case studies of how companies that have made these technologies a cornerstone of their clinical development strategies are reducing them to practice.

The benefits of digital endpoints over traditional clinical metrics are now well understood. Not only can they provide more objective, granular and frequent measurements of patient outcomes, often by capturing daily activities that are more relevant to patients' quality of life, they can do so from the comfort of patients' own homes.

But turning digital technologies into meaningful trial instruments, and changing established practices to incorporate them into clinical development programs, remains a question of risk-taking, and of who will lead the way.

Cadavid's career sourcing and developing digital endpoints at Verge, Fulcrum Therapeutics Inc. (NASDAQ:FULC) and Biogen Inc. (NASDAQ:BIIB) has largely aligned with the areas where digital endpoints have gotten the most traction: measuring movement or sleep for diseases characterized by loss of neuromuscular function.

The digital endpoints he has worked with span the clinical development continuum, ranging from digital metrics of remyelination for multiple sclerosis (MS) and optic neuritis at Biogen, to Fulcrum's pivotal Phase III study for facioscapulohumeral muscular dystrophy (FSHD), from which top-line data are due 4Q24. His most recent experience has been launching Verge's Phase Ib proof-of-concept study for amyotrophic lateral sclerosis (ALS), which kicked off last month.

Cadavid told BioCentury that Fulcrum's decision to use the "reachable workspace" metric, which he co-developed based on technology from University of California Irvine researchers, as a primary endpoint in its pivotal trial was a special case of a new technology filling a void, since there is no established Phase III endpoint for FSHD. Reachable workspace captures upper body muscle function using the Kinect device, a sensor for the Xbox video game console developed by Microsoft Corp. (NASDAQ:MSFT).

In general, he does not think using digital technologies to influence regulatory decisions should be the field's top goal.

"I attended a conference with developers of digital endpoints, and they're all obsessed with Phase III, but that's not where the need is," Cadavid said.

Instead, he believes digital technologies will have their greatest impact as "better endpoints early in development, so you go into Phase II with confidence."

Cadavid thinks the accuracy digital technologies provide enables better target validation and dose-finding than traditional endpoints used for regulatory decision-making, which tend to be blunter instruments.

"Early on, it's not about power. It's about precision," he said. "If we have a good drug that works, then later we can use the endpoint FDA likes."

A May 2023 analysis of a library of digital endpoints compiled by the Digital Medicine Society (DiMe) showed digital endpoints are most commonly incorporated into Phase II trials and postmarket studies. Out of 216 clinical trials with digital endpoints, only eight (4%) were Phase I studies.

Verge is prioritizing digital endpoints tracking movement and voice in its early-stage ALS trial. According to Cadavid, that decision was met with hesitancy by some investors and business development executives.

"People are very stuck to the old way, which generates fear. They say, 'everyone else is using a Phase III endpoint.' We're also using that, but not to make decisions" in early trials, he said.

Throughout Cadavid's career, finding the right digital endpoints has been less about finding vendors selling perfect, ready-made solutions than about determining what the company needs to measure, and then surveying the landscape of academics and companies to see "who has done enough work that I can take a technology into proof of concept as an endpoint," he said. In some cases, the technology had been developed for completely different applications, without clinical trials in mind.

Cadavid said drug developers should stay focused on the most impactful endpoints for their program, which could be just a small subset of what digital device makers can measure, especially if those extra measurements come with greater privacy concerns.

He added that it's important to "lock" the hardware and software being used in a trial, even if those versions are soon outpaced. "Developers of digital devices always want to improve them. That's good, but it doesn't work for drug development."

## "EARLY ON, IT'S NOT ABOUT POWER. IT'S ABOUT PRECISION."

### DIEGO CADAVID, VERGE

### Movement and voice

To assess treatment-related changes in ALS, Verge sought to measure voluntary movements.

"Everything that happens in the disease is because voluntary muscles are denervated," Cadavid said. "What are the digital endpoints that exist, and are robust, reliable and user-friendly?"

At Fulcrum, Cadavid had worked with a Massachusetts Institute of Technology team led by Dina Katabi, co-founder of Emerald Innovations Inc., which developed a touchless, wireless environmental sensor that tracks movement and breathing, including during sleep. It was originally developed as an at-home safety monitor for seniors that doesn't require wearing or charging a device.

The technology measures radio waves that bounce off a person's body, and uses machine learning algorithms to extract movement trajectories and breathing patterns. Patients wear a band for a week or two to help the device learn to distinguish their movement patterns from other people in the house. "I told them, what you have is perfect for clinical trials," Cadavid said.

Fulcrum and Emerald tested the technology in FSHD patients, and published the results in 2020. The companies measured functional deterioration over three months by capturing slow declines in the time it took patients to get out of bed every morning.

"The tool was so precise, you could actually detect a real change," Cadavid said. "I then came to Verge and thought, ALS is perfect for this."

In May, Verge announced a partnership with Emerald to place these sensors in the homes of ALS patients in the Phase Ib trial of its lead candidate, VRG50635. The small molecule is an inhibitor of PIKFYVE, a lipid kinase in the endolysosomal system.

Other companies using Emerald's device in clinical trials include Aspen Neuroscience Inc. and the BlueRock Therapeutics subsidiary of Bayer AG (Xetra:BAYN).

Cadavid said the company has gotten many questions on privacy from regulators, particularly in Europe, but no institutional review board rejections. He said the reams of

radio wave data the device detects are not interpretable by humans, and require Emerald's specialized machine learning algorithms to deconvolute.

Verge's second digital endpoint, which detects speech and language patterns, comes via its partnership with Modality.AI Inc., announced in November.

Modality.AI is developing its platform for more than a dozen indications, of which ALS is the second-most advanced, with 15 peer-reviewed publications. The company's technology is part of the Austen Speech Study run by patient-focused non-profit EverythingALS, which has created a resource of 12,000 hours of audio and visual data from a cohort of 850 ALS patients to support digital biomarker development; the data were made public on Jan. 30.

In Verge's study, each patient is provided a web-connected tablet through which they interact with an avatar named Tina every two weeks, answering questions and performing phonic repetitions. Analysis of the recordings captures changes in speech over time.

Cadavid said Verge opted not to use every feature that Modality.AI offered, partially for patient privacy reasons. "They had options for facial expressions, but all we're capturing are voice samples."

Verge's study will also use actigraphy, the acceleration-detecting technology used in smartwatches, to sample patient mobility outside the home one week per month via sensors on patients' backs and wrists. "Multiple sclerosis trials started using actigraphy 15 years ago. ALS is in the Middle Ages," said Cadavid.

Verge hopes the data will not only give the company insight into whether its therapy is having the intended effect, but also assess dose responses, and help it to home in on the best dose.

Recent drug approvals for ALS have raised discussions about endpoints for the disease, and whether they are sensitive enough to capture treatment effects in the highly heterogeneous population.

The questionnaire-based ALSFRS-R score, the basis for FDA's 2022 approval of Relyvrio from Amylyx Pharmaceuticals Inc. (NASDAQ:AMLX), has been the dominant endpoint in ALS. While it measures a wide variety of activities that patients care about, the coarseness and subjectivity of the scale can make it difficult to reliably detect treat-induced changes.

Plasma levels of the axonal protein NfL became an "anchor biomarker" last year via FDA's accelerated approval of Biogen's Qalsody tofersen, which used the metric as a surrogate endpoint. A marker of axonal degeneration, plasma NfL offers an opportunity to accelerate research on other biomarkers, and see how they relate to neuronal survival.

## "MULTIPLE SCLEROSIS TRIALS STARTED USING ACTIGRAPHY 15 YEARS AGO. ALS IS IN THE MIDDLE AGES."

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Cadavid said plasma NfL measurements will be key for validating VRG50635's mechanism of action. "We think our drug will alter the death of motor neurons. If it doesn't, our hypothesis is incorrect."

### Kinecting the dots

The reachable workspace endpoint that Cadavid's Fulcrum team co-developed for the company's FSHD trials is a case study in building a regulatory-grade digital endpoint from scratch.

FSHD is an autosomal dominant genetic disorder caused by mutations in transcription factor DUX4 that promote its aberrant expression in skeletal muscle, leading to muscle weakness in the face, shoulder girdle and arms.

Patients undergo physical therapy, and are prescribed drugs to manage specific symptoms, but there are no marketed therapies targeting the root cause of disease. Fulcrum's Phase III-stage losmapimod, a small molecule p38 MAPK inhibitor that decreases DUX4 expression, is the most advanced of eight FSHD programs in the clinic.

The Fulcrum team collaborated with UC Irvine physiatrist Jay Han, who had developed a technology that tracked the function of the shoulder using the contactless Kinect 3D motion sensor, first published in 2015. Originally developed to facilitate game play on Microsoft's Xbox console, Kinect uses an infrared and RBG cameras to sense depth and capture postural and movement information.

Seated in front of the sensor, patients undergo a series of protocol-directed arm motions, with and without weights, and their upper limb trajectories across five spatial regions are quantified via the reachable workspace metric.

Because there are no drugs approved for FSHD, there was no established Phase III endpoint, leaving room for a new metric, and incentive to invest in its development, Cadavid said. "Why don't we advance this endpoint to be what a regulator wants, in case it's good for Phase III?"

Doing so involved qualifying the device with FDA and EMA, obtaining a European CE mark for it, and creating a company, Bioniks, which is commercializing the technology under the name Kinetigram.

Fulcrum and its collaborators also did work to relate the digital endpoint to outcomes that were meaningful for patients and clinicians.

According to a January corporate presentation from Fulcrum, a longitudinal natural history study of 16 FSHD patients showed annual reachable workspace declines of about 3% compared with baseline, and the metric correlates with the ability to perform daily living activities such as eating and changing clothes, and with patient-reported outcomes metrics such as Neuro-QoLUpper Extremity (NeuroQoL-UE).

In Fulcrum's Phase II ReDUX4 trial, the primary endpoint was change from baseline in DUX4 activity by muscle needle biopsy, and reachable workspace was one of several secondary endpoints. While the trial did not reach its DUX4 activity endpoint, it showed losmapimod preserved and improved function as assessed by reachable workspace, and had a durable effect on the endpoint at 96 weeks in an open-label extension study.

"The Phase II trial showed remarkable results. In both the dominant and non-dominant shoulder, it arrested progression, and improved function," Cadavid said.

Based on discussions with FDA and EU regulatory agencies, Fulcrum made reachable workspace the primary endpoint of Phase III REACH trial, though the agency reserves the right to make a final decision later on. "FDA is open to innovation, but you have to follow their guidelines, and reach out ahead of time," said Cadavid.

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