Industry embraces virtual trial platforms

Site-less trials promise to speed up drug development — but obstacles to in-home data collection abound.

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Novartis is doubling down on the strategy of running remote drug trials that are untethered by geographical limitations and allow people who live far away from medical research centres to take part in clinical studies. In March, the company announced it was teaming up with Science 37, a company that specializes in running these 'virtual' studies, to launch up to 10 trials over the next 3 years.

Novartis was an early backer of Science 37 through a venture investment arm, and had already worked with the company to introduce a virtual element to a handful of ongoing trials of experimental and approved medicines being evaluated for new indications. According to Badhri Srinivasan, head of Global Development Operations at Novartis, the company will now take lessons learned from those initial studies to increasingly blend digital and traditional trial designs, with the goal of eventually going completely site-less for disease settings such as dermatology and neuroscience, in which home-based data collection is feasible and where continuous, real-time monitoring is desirable.

"It's a great catalyst to increase trial participation," Srinivasan says. "We definitely see site-less trials in some shape as a key component of how we do clinical trials of the future."

Novartis is far from alone. Nearly every major pharmaceutical company is now experimenting with decentralized trials that use the internet to recruit patients and smartphones and wearable devices to collect data. With an estimated three-quarters of the global public saying they'd be willing to take part in a clinical trial, but only a tiny fraction ever bothering to do so, part of the idea is to make it easier for volunteers to engage with the clinical research enterprise. But virtual trials also promise faster patient recruitment timelines, low-cost data collection and new outcome measurements.

"We're on the verge of a transformative moment in drug development," says David Reese, head of Translational Sciences at Amgen. "Over the next decade, you will see a very substantive change in the clinical trial enterprise that is enabled by new technologies."

Remote possibility

The first major pharma-backed foray into internet-based trials occurred in 2001, when Eli Lilly tested its then-experimental erectile dysfunction drug tadalafil by having participants fill in questionnaires online. The study also involved in-person visits to investigator-run clinical sites, however, and it would take another decade before Pfizer launched the first-ever truly virtual trial.

The REMOTE trial, started in 2011, was designed to mimic previous clinic-based trials of an extended-release formulation of tolterodine for overactive bladder problems. Aspects of the study, such as web-based informed consent and data collection, worked well, says Craig Lipset, head of Clinical Innovation at Pfizer. But the overall protocol proved onerous, with multistep enrolment criteria that necessitated laboratory testing and physical examinations with community doctors. Ultimately, only 18 of the more than 5,000 women who started the screening process actually made it to the drug randomization stage.

Lipset sees two key lessons from the REMOTE trial. First, the marketing of the trial was completely decoupled from how would-be participants managed the rest of their health. "We failed to appreciate the importance of engaging patients together with their treating physicians," he says.

Second, the rigid trial protocol failed to put the interests of the participants first. Newer user interfaces such as Science 37's NORA platform — short for Network Oriented Research Assistant — could help. But until people become more comfortable with virtual platforms, it's best to offer a mix of options rather than going completely virtual, says Tomasz Sablinski, co-founder and CEO of digital clinical service company Transparency Life Sciences. "We have to take baby steps," he says.

Genentech recently adopted that kind of hybrid approach for a head-to-head trial of rituximab and the immunosuppressant mycophenolate mofetil for a rare skin-blistering disease called pemphigus vulgaris. The 124-person trial involved a single telemedicine-based site managed by Science 37, and more than 60 physical sites around the world. Noah Craft, co-founder and CEO of Science 37, says his virtual site was by far the quickest recruiter, enrolling 10 participants in the same time as it took 21 average physical recruitment sites to find 10 patients.

This speed was again on display last year when Science 37 completed a 372-person, placebo-controlled trial of a topical probiotic spray for mild-to-moderate acne on behalf of AOBiome. Todd Krueger, AOBiome's CEO, says that the study lasted less than 12 months, much faster than anticipated. "If they can shave 6 months off a trial, that's 6 months of burn a company like ours doesn't have to go through waiting around for data."

Craft credits the company's in-house marketing team for much of that recruitment success. Science 37 finds most of its study subjects by advertising on Facebook and through Google AdWords, although it also works with patient advocacy groups on some enrolment efforts. The company tracks how its ads are working and what times of day get the best hit rate, and adjusts its recruitment campaigns accordingly.

Science 37 then sends iPhones to all study participants and runs its trials through a mix of remote data collection and telemedicine visits with company-affiliated physicians.

In Craft's view, that extra human factor was the key missing piece in earlier failed virtual trial efforts. "We combined a high-tech, high-touch approach where we actually have the doctors and technology under one company," he says. Unlike conventional contract research organizations or other companies with remote data capture technologies, "we are the actual organization of doctors that are responsible for clinical care."

Big data analytics

Science 37's success to date suggests that virtual trials might offer benefits over site-based ones. But these trials worry legal scholars like Lori Andrews of the Chicago-Kent College of Law. "Online recruitment based on information acquired through non-transparent practices also threatens individual privacy rights, the well-being of participants, the integrity of the trial process and ultimately the health of the public," Andrews and her colleagues wrote in the *Journal of Health Care Law & Policy* last year.

Those privacy concerns could be especially pronounced following recent revelations of improper data collection by third parties from tens of millions of Facebook users.

Industry will also have to allay fears that a reduction in doctors' visits may jeopardize patient safety.

But perhaps the biggest obstacle comes from company executives, many of whom remain unconvinced that the quality of data collected by self-reporting tools and wearable devices is up to snuff. "That's one of the critical stumbling blocks now," says Ken Getz, who studies site management and patient recruitment at the Tufts Center for the Study of Drug Development. "That's where a lot of sponsor companies are reluctant to jump into this initiative with both feet, because they're really waiting to get a better feel for how valid that data is and whether they can trust in it."

To get a feel for this, Amgen recently enlisted 78 migraineurs to wear Apple Watches loaded with a migraine-tracking app. It is now assessing 3 months of data to see whether an algorithmic analysis of step counts and heart rate provides a more reliable outcome measure for migraine trials than self-reported headache diaries. If validated, Reese says, Amgen may use wearable smartwatches for at-home measurements in future studies of its phase II PAC1-targeting monoclonal antibody AMG 301.

Janssen is similarly trying wearables on for size. In 2015, the Johnson & Johnson subsidiary teamed up with the Scripps Translational Science Institute and with Aetna, a major US health insurer, to run a home-based trial for stroke prevention.

The trial investigators, led by Scripps cardiologists Steven Steinhubl and Eric Topol, used Aetna's medical claims records to find around 360,000 patients at increased risk for irregular heartbeat. They then emailed or wrote to 100,000 of these individuals, and found 2,655 people willing and eligible to participate in a trial designed to test whether a wearable wireless electrocardiogram patch could help diagnose atrial fibrillation more effectively than standard clinical care. As reported at this year's American College of Cardiology Scientific Sessions, around 5% of participants were diagnosed with the heart condition within 4 months of wearing the patch, compared with less than 1% in a control group that received only routine care.

"We showed this model to be exceptionally frugal, fast and effective," says Topol.

Equally informative to executives at Janssen were some of the logistical challenges that the trial identified. Most notably, over one-third of the trial participates never once stuck the heart-monitoring devices on their chests. That echoes the finding of Pfizer's earlier REMOTE trial, and suggests much more still needs to be done to keep patients on protocol over the course of a site-less trial.

"The challenge of patient engagement has not gone away," says Dmitri Talantov, head of Medical Affairs for Clinical Innovation at Janssen. "It's just been transformed."

Virtual gaming

One strategy employed by EmpiraMed to aid with engagement is to add game-like elements to trial participation. Rather than simply giving out money for completing certain study milestones, as a conventional trial might, EmpiraMed's post-marketing virtual trials offer points for each and every aspect of participation, from logging in to the platform, to filling in a questionnaire or uploading data from wearables. The points can then be cashed in for gift cards or donated to disease charities. "We make it fun," says EmpiraMed CEO Greg Erman, who claims that gamification improves retention rates.

More broadly, all the new digital efforts are attempting to refocus the clinical trial on the patient experience, says Kathy Hudson, executive director of the People-Centered Research Foundation. "We're taking what the high-tech world has known for a long time about user-centred design and trying to apply it to medical research."

Yet, even with slicker apps and better mobile platforms to come, remote trials will fail to address the most fundamental problem plaguing clinical research today, says Jason Bobe, who studies patient engagement at the Icahn School of Medicine at Mount Sinai. The bigger overall problem is that industry still treats patients more like study subjects than like active participants.

"No matter how convenient it is, these trials are often in the interests of the investigators and sponsors and not the consumers," Bobe says. "We're not going to escape that there's a business side of medicine, but we have to figure out how we can also inspire people to participate in research on terms that are equitable for them."