A still from the virtual reality system gameChange — developed to treat people experiencing psychosis.

UNIVERSITY OF OXFORD/OXFORD VR

THERAPY

A smarter way to treat

With ageing populations forcing health-care systems to become more efficient, the treatment of many common physical and mental ailments is going digital.

BY SIMON MAKIN

I'm standing in a doctor's waiting room. A few distressed-looking people are seated on chairs lining the walls. I turn around to see a man blocking the entrance behind me. Suddenly, I hear the receptionist exclaim as several paper slips are blown by a fan into the air above my head. I grasp them and return them to the reception desk.

For a moment, I consider walking over to the other side of the room. But this isn't real. I'm actually in the office of clinical psychologist Daniel Freeman at the University of Oxford, UK, wearing a virtual reality (VR) headset and brandishing a motion-tracked controller in each hand. Were I to attempt to explore, I'd run into one of the very real walls of Freeman's office — or worse, his computers.

The scene before me is one of several scenarios that make up gameChange — a VR system that Freeman and his colleagues are developing to treat psychosis. Because people experiencing psychosis often think bad things will happen in social situations, such as people trying to hurt them, they withdraw socially, leading to isolation and strengthening of their beliefs. The idea behind gameChange is to put people with psychosis in simulations of the situations they fear, to help them to learn they are safe and, hopefully, to relieve their symptoms generally.

GameChange is at the advanced end of a spectrum of therapies that use digital technology to prevent, manage and treat health conditions. As well as VR, the rapidly expanding field also includes online therapies to help people to adopt healthy behaviours, and social robots and smart pills that boost the effectiveness of prescription drugs by improving people's adherence to dosing guidelines. Such technologies have the potential to transform both physical and mental health care. But as the number of platforms and devices claiming to provide health benefits balloons, medical regulators and industry groups are scrambling to ensure that standards of clinical evidence are met.

REMOTE GUIDANCE

"Digital therapeutics have been on the market for about ten years, but there's only been a few of them," says Megan Coder, executive director of the Digital Therapeutics Alliance (DTA), headquartered in Arlington, Virginia. Launched in 2017, the alliance is a global non-profit trade association that aims to set standards and promote integration into health care. "We look at

the best practices and core principles all these products should abide by," she says.

One of their first tasks was providing an official definition to distinguish digital therapeutics from other digitally driven health innovations such as telemedicine. "Digital therapeutics are part of the broader digital-health landscape, but in order to be called one, a product has to be software driven, evidence-based, and make a claim to prevent, manage, or treat a medical disease or disorder," says Coder. "They're different than diagnostics, telehealth, and all these others." The devices can be used alone, or with other therapies to optimize outcomes.

One of the earliest advocates for digital therapeutics was Joseph Kvedar, a dermatologist at Massachusetts General Hospital in Boston who in 1995 was tapped to lead Partners Connected Health, a joint initiative with the nearby Brigham and Women's Hospital, to explore the development and application of technology for delivering care outside the hospital or doctor's office. Like many in the field, he is motivated by the need to care for an ageing global population. He says that "2020 is a watershed year in the history of mankind". By then, there will be more people over 60 than under 5. People are living longer, but they are not staying healthy for those extra years — and the medical profession cannot keep pace. "The solution to that is what I call the one-to-many model of care," Kvedar says. The idea is to extend physicians' reach by overcoming time, place and personnel constraints that limit health-care delivery. It's about access, convenience and efficiency, says Kvedar. "It's more convenient to get care where you are, when it's needed; it's more continuous," he says. "We can take better care of you with fewer resources, using this kind of approach."

An area of particular interest is the capacity of digital technology to effect behaviour change at large scales. "We know from non-medical phone use how addictive apps can be," Kvedar says. "How can we use that to change behaviour in the space of chronic illness?"

One of the earliest, and still most prevalent, examples of digital delivery of behavioural interventions has been in diabetes care. In 2002, a study[1] showed that an intensive behavioural intervention targeting diet and exercise could significantly reduce people's risk of developing type 2 diabetes. In the United States, the finding has led to the development of numerous lifestyle-change programmes that are accredited and promoted by the US Centers for Disease Control and Prevention (CDC). Most of these CDC-recognized programmes involve face-to face communication, just as the 2002 study did. But some companies, such as Omada Health in San Francisco, California, have sought to deliver the intervention digitally — and in so doing, reach more people. "The vision with Omada was: how do you take those evidence-based behavioural treatments, done in traditional clinical face-to-face settings, and make them infinitely scalable and accessible to millions of people?" says Cameron Sepah, a behavioural health psychologist who spent five years with Omada between 2012 and 2017.

Omada's programme involves a year-long educational curriculum, personalized health coaching and support through a small peer group using a social network. It also uses connected devices to track people's nutrition, activity and weight. "It's hardware, software, human coaching over a long time span; it's throwing the kitchen sink at people," says Sepah, who is now a venture capitalist. In 2017, Sepah and his colleagues reported[2] that, after three years, participants with higher than normal blood sugar on enrolment maintained a reduction in blood sugar, as determined by A1c, the blood test commonly used to diagnose and monitor diabetes. "On average, people regressed from the prediabetes range to the normal range, which is pretty impressive," says Sepah. They also maintained an average 3% loss of body weight. "We shared our results with the CDC, and they eventually approved online programmes as being comparable to in-person programmes," says Sepah. The CDC now fully recognizes online diabetes-prevention programmes that meet its criteria from 14 providers.

Omada plans to move into management of existing diabetes, an area in which some companies have made headway already. Digital-health company Welldoc, based in Columbia, Maryland, has BlueStar — an app that helps people to log their blood glucose, medications, activity, diet, blood pressure and weight, either manually or through Bluetooth-enabled gadgets. The data can then be shared with the person's care team. "They showed they could lower A1c by two full points in patients with high enough A1cs," says Coder. This is a greater effect than drugs typically manage. "The fact their product outperformed that of a drug caught a lot of people's attention," she says.

"We know from non-medical phone use how addictive apps can be."

Digital delivery of behavioural therapy is not limited to diabetes, or even physical health. More and more digital therapeutics are emerging that tackle mental health. The most common application is digital delivery of cognitive behavioural therapy (CBT) for depression and anxiety disorders, but the area is diversifying rapidly. Pear Therapeutics in Boston partnered with Sandoz, a division of Swiss pharmaceutical company Novartis, to develop an app called reSET that delivers CBT for substance-abuse disorder. Pear also has plans to develop a product for schizophrenia, and is collaborating with the University of Virginia in Charlottesville to develop a treatment for insomnia and depression, called Somryst. The leading player in this area is currently London- and San Francisco-based digital-health company Big Health. Its Sleepio system is an online self-care programme based on CBT for insomnia, which has been shown to improve both insomnia symptoms and mental well-being.

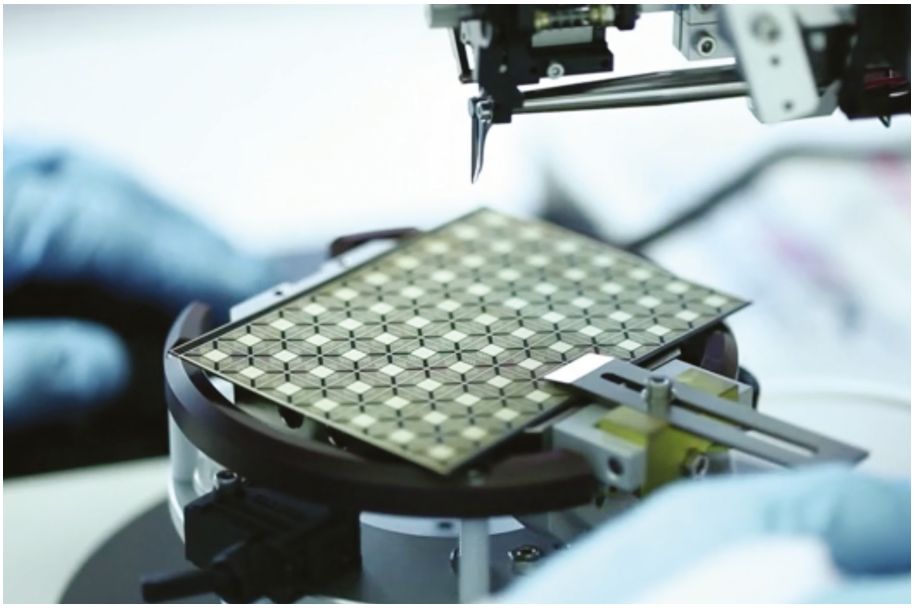
Whether treating physical or mental health, developers need to take care that the design of their interventions does not wholly displace the human contact that is an essential part of health care, says Kvedar. "If you use technology in a way that people feel less cared for, they typically don't like that," he says. For some applications, including therapy for complex problems such as trauma, digital solutions might not be able to replace face-to-face therapy. But, says Eva Papadopoulou, a psychologist and implementation manager based in London at digital mental-health company Minddistrict, replacing therapists is not the aim. "What we want is to release capacity for therapists and care teams to focus on the people who need them most," she says. "There's a massive campaign to battle stigma and have people coming forward, then we don't have the people to help them."

DIGITAL DRUGS

As well as being treatments in their own right, digital therapeutics are also proving useful in helping people to gain the maximum benefit from conventional pharmaceutical therapies. "Efficacy is what a drug can do; effectiveness is how it works in the real world, and right now we have a large efficacy–effectiveness gap," says George Savage, a physician and co-founder of Proteus Digital Health in Redwood City, California. The main issue is that, worldwide, between one-quarter and one-half of people do not take their medications as recommended. In the United States alone, this has been linked with 125,000 deaths and is estimated to cost up to US$289 billion annually. "We have the potential to get a lot more value out of existing medical treatments," says Savage. "It strikes me as low-hanging fruit."

Provisions in the Affordable Care Act to make reimbursement dependent on outcomes, have given health-care providers in the United States an incentive to tackle adherence. Together with the adoption of electronic health records (see page S114), this has driven an explosion in the field, Kvedar says. One effort, developed by Catalia Health in San Francisco, is a robot called Mabu, the main purpose of which is to nudge people to take their medications. More than a simple medication-reminder system, Mabu uses artificial intelligence and psychological modelling to tailor conversations to individuals and build relationships with them, to keep them adhering to dosing regimens for longer. Mabu is currently being used for people with kidney disease, rheumatoid arthritis and congestive heart failure, but Catalia plans to adapt it for other conditions.

Another approach to reducing non-compliance is to make the pills themselves report when they are taken. Savage, Proteus



PROTEUS DIGITAL HEALTH

A sheet of Proteus's ingestible sensors. Each sensor is the size of a grain of sand.

co-founder and engineer Andrew Thompson, and their colleagues have developed an ingestible sensor that can be incorporated into pills. The sensor is the size of a grain of sand and coated on one side with copper and on the other with magnesium. When a pill is swallowed, the liquid in the stomach connects the two sides, generating an electrical signal that can be picked up by a sensor patch worn on the person's skin[3]. A digital record is sent to a mobile app and, with the person's consent, shared with health-care providers.

"By building in feedback and engaging the patient, they can do a better job of taking the medication," says Savage. "And, as importantly, the physician can discern between failure to respond and failure to adhere, and therefore make a better next decision." The patch also monitors the user's activity, heart rate, sleep quality and temperature, which means it can record people's responses to the medication. "You can think of this as a digital nurse," Savage says.

Proteus's system is currently used to monitor people with type 2 diabetes, hypertension and hepatitis C, with investigations under way for its use in HIV prevention and treatment. The company is also beginning studies of potential applications in oncology. "Quite often, cancer drugs carry very challenging dosing schedules," Savage says. "We expect patients to do all this perfectly with no feedback, no measurement, no cues, no rewards, nothing." Digital-health company etectRx in Gainesville, Florida, has developed a similar system using radio technology; others have developed systems that log injections for multiple sclerosis and inhaler activations for asthma and chronic obstructive pulmonary disease.

Technologies such as these could also allow people to access drugs that they would usually struggle to get. People at high risk of non-adherence, such as homeless people, are typically denied access to expensive treatments. In a pilot study, 28 high-risk patients were given treatment for hepatitis C that incorporated Proteus' technology. On average, 94% of prescribed doses were taken, and 26 participants were cured[4]. "We got a very high cure rate in a very challenging population," says Savage.

VIRTUALLY TREATABLE

Improvements in VR technology and falling costs are raising hopes that its use might become more widespread in medicine. "VR has been used for 25 years, but only for very few conditions, in specialist centres," says Freeman. The technology has seen most use in delivering exposure therapy for post-traumatic stress disorder, and this is still the leading application. But it also has potential uses in depression, anxiety, phobias, obsessive–compulsive disorder, eating disorders, addiction and psychosis.

Freeman is currently investigating its use for treating schizophrenia. Initially, he used VR as a research tool to assess paranoia by presenting people with neutral social situations and seeing whether they perceived hostility. Now, he is aiming to use simulation to allow people to learn by experiencing real-world situations. "The really good treatments aren't talking therapies, they're action therapy," says Freeman. "You go into situations and learn how to think, feel and act differently."

The gameChange clinical trial, which launched in July, is the largest trial of a VR therapy for schizophrenia so far. Participants first choose from six scenarios, such as visiting a pub or catching a bus, that were proposed by a patient group coordinated by mental-health charity The McPin Foundation in London, which promotes the involvement of people with mental-health conditions in research. The 432 participants then set some parameters for the session, including how challenging they want it to be, which affects the numbers and proximity of other people. Additional stressors can also crop up, such as the papers that blew into the air as I stood in the doctor's waiting room.

After three hours of self-paced treatment, researchers will assess participants' avoidance and distress in real-life situations, and again at a six-month follow-up assessment. As with other digital therapeutics for mental-health disorders, however, the aim is to supplement clinicians, not replace them. "We need more therapists, not fewer," says Freeman. "But given the numbers of people who aren't getting the help they need, we're going to need solutions like VR." And with consumer systems becoming cheaper and more widespread, Freeman hopes that therapy could ultimately be delivered in a person's home. "That would be a very appealing way to access help," he says.

REGULATION QUESTIONS

As digital treatments proliferate, the need for scrutiny of the various medical claims being made becomes ever more important. "You have the App Store, which has something like 300,000 health apps, but doctors are afraid they're going to recommend the wrong one," says Kvedar. "Some of them have high-quality clinical research behind them, some do not, and the regulatory bodies in the United States are struggling to keep up with the volume to make sure no one is making false claims."

The DTA industry group, which companies join voluntarily, expects members to adopt certain principles and best practices, to reassure users that they take robust evidence and regulatory clearance seriously, says Coder. "That's part of our goal as an alliance, to ensure companies know that these are the standards for our industry," she says. These include publishing trial results with clinically meaningful outcomes in peer-reviewed journals, and incorporating adequate privacy and security protections.

Digital therapeutics can also run into government regulation. In the United States, they usually fall under the Food and Drug Administration's (FDA's) definition of a medical device, which is anything other than a drug that is "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease". Most must therefore follow the regulatory pathways set up for medical devices. In these cases, "the FDA applies regulatory oversight since they could pose a risk to patient safety should they not function as intended", says Coder.

The precise path a digital therapeutic must take, and the level of clinical evidence its maker must provide, is dependent on the novelty of the product and how great a risk it poses should it malfunction. WellDoc's type 2 diabetes management tool, BlueStar, was granted FDA approval in 2010. Because BlueStar was similar to existing therapies, this involved

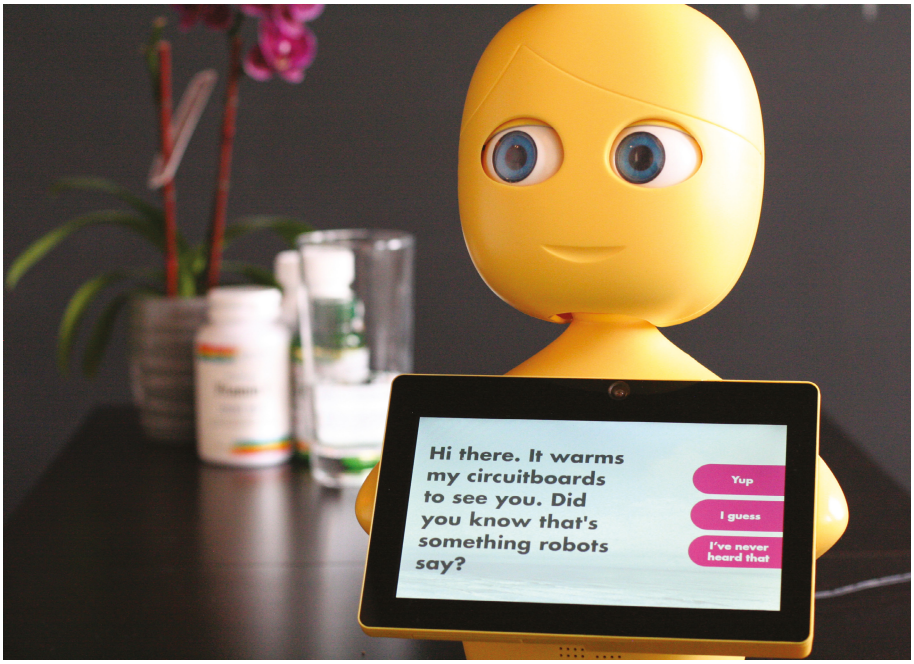
providing evidence of 'substantial equivalence' to existing diabetes-management software, rather than new clinical evidence. Entirely new therapies, however, typically face bigger hurdles. Pear's reSET, for instance, had to submit results of a randomized controlled trial (RCT) through the FDA's *de novo* approval pathway. The FDA approved it as a prescription-only product, a designation that is independent of the level of regulatory control a digital therapeutic requires.

However, almost regardless of the type of claim being made, the FDA can exercise 'enforcement discretion' — waiving regulatory oversight if it decides a product is low risk. For example, apps that aim to prevent diabetes by helping people to change their diet and to exercise, such as Omada's programme, can be marketed in the United States without providing safety and efficacy evidence to the FDA.

For those digital therapeutics that do have to take the long road, the process is not a rapid one. "An RCT takes about three years, in which time there's been new research and evidence published, and we have improvements," says Papadopoulou. "All the digital providers say it's too slow," she adds. "The digital world moves fast." Iteration after approval can also be a pain point. "You can't change your product so much that it's no longer doing what it was cleared to do," says Coder.

The FDA's regulatory pathways for medical devices took shape in 1976, and the agency has acknowledged the need to modernize its procedures to better foster innovation, particularly in light of the iterative nature of digital products. In December 2017, the FDA issued new guidelines clarifying types of product that will no longer be deemed regulated medical devices, such as apps that promote general wellness. The guidelines also outline the kinds of change to existing software that will require fresh approval, and those that won't. Earlier that year, it also outlined a pilot scheme for a 'pre-certification' programme that assesses companies, rather than products. Pre-certified companies deemed to have demonstrated excellence in software development and validation could market lower-risk devices without further oversight, or through a more streamlined process. Real-world performance data, which are generally much easier to collect for digital therapeutics than for pharmaceuticals, could then be used to affirm a product's regulatory status, as well as supporting its evolution. The idea is being tested in a pilot scheme involving nine companies that are undergoing the new process alongside conventional review, to check that they produce the same decision. One of those participating is Pear, that in July became the first company to apply for authorization through the scheme, for Somryst.

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) assesses the clinical and economic efficacy of treatments. Although commissioners in the country's National Health Service (NHS) are not bound by NICE recommendations, they carry enormous weight. In an effort to accelerate NHS uptake of digital innovations, NICE, in collaboration with stakeholders such as NHS England and NHS Digital, published guidelines last year aimed at helping manufacturers to understand the kinds of evidence they should be providing, and what commissioners should be requesting. "The NHS has done a fantastic job with their evidence-for-effectiveness guidelines," says Coder. It provides guidance for classifying a product according to its function or the type of claim being made, with corresponding recommendations for minimal and ideal types of supporting evidence, as well as appropriate economic data.



CATALIA HEALTH

Catalia Health's Mabu uses AI to build relationships with patients, helping them to stick to drug plans.

"The NHS has done a fantastic job with their evidence-for-effectiveness guidelines."

NICE is also working with the NHS to expand its provision of digitally enabled therapy for common mental-health conditions, such as depression and anxiety disorders, through a new assessment programme. To be eligible, the digital treatment must mirror a NICE-recommended psychological therapy for the relevant condition, be designed to be used with therapist assistance, and be backed by at least one RCT. NICE assesses content, evidence, and cost and resource impact, before potentially recommending a treatment for 'evaluation in practice', where performance will be assessed during use in NHS services. The scheme aims to assess up to 14 treatments by March 2020. Twelve assessments have been published so far, of which three recommended the therapy for evaluation in practice: Space from Depression, for depression, from SilverCloud in Boston, which is currently one of the biggest providers of digital mental-health treatments to the NHS; Deprexis, also for depression, from GAIA in Hamburg, Germany; and BDD-NET, for body dysmorphic disorder, developed by researchers at the Karolinska Institute in Stockholm. Another digital therapeutic from the Karolinska Institute — OCD-NET, for obsessive–compulsive disorder — was also assessed, and although not accepted yet, the researchers were encouraged to apply for development funding from NHS England to address some technical issues, including around security and privacy, that the assessors had identified.

With gameChange still in its early days, Freeman and his colleagues have all this to come. They are attempting to get a head start, however, by involving the NHS early on. The team is assessing the system's cost-effectiveness and overall value to the NHS. "We're talking to commissioners and staff in services, and collecting a lot of health economic data," says Freeman. But he is not just looking for cost savings. Like many developers of digital therapeutics, he wants the system to provide a transformational shift in how health care is delivered. "GameChange could show how you can automate psychological treatment and get it out to health-care systems at scale," he says. "If we crack that, it will show the way for many other conditions. That's the hope." ■

Simon Makin *is a science writer based in London.*

1. Diabetes Prevention Program Research Group *N. Engl. J. Med.* **346**, 393–403 (2002).
2. Sepah, S. C. *et al. BMJ Open Diab. Res. Care* **5**, e000422 (2017).
3. Hafezi, H. *et al. IEEE Trans. Biomed. Eng.* **62**, 99–109 (2015).
4. Bonacini, M. *et al. Open Forum Infect. Dis.* **5**, S656 (2018).