How Digital Therapeutics Developers Can Satisfy Diverse Stakeholder Needs
“It’s not about can digital help medicine. It’s about can digital be medicine.”

- Eddie Martucci
  Co-founder and CEO
  Akili Interactive
Introduction

If there are lingering doubts about the viability or market potential of digital therapeutics (DTx), recent moves by the U.S. Food & Drug Administration should lay them to rest. In December 2018, Pear Therapeutics and its partner, Novartis’ Sandoz unit, received FDA clearance for reSET-O, a prescription-only mobile medical app that helps patients with opioid use disorder remain in outpatient treatment programs. The same month, with support from regulators, the ECG app on the Apple Watch 4 became the first direct-to-consumer product that can notify users of an irregular heart rhythm.

While these two examples stand out, there are dozens of other software-driven products under regulatory review for diagnosing, treating, or preventing medical conditions. As Sandoz CEO Richard Francis said in a press release announcing the reSET-O, digital therapeutics “have the potential to fundamentally change how patients interact with their therapies,” and may represent “the next chapter of medical innovation.”

Defining DTx:

“Digital therapeutics deliver evidence-based therapeutic interventions to patients that are driven by high quality software programs to prevent, manage, or treat a medical disorder or disease. They are used independently or in concert with medications, devices, or other therapies to optimize patient care and health outcomes.”

- Digital Therapeutics Alliance

Now, global regulatory bodies seem poised to weave DTx into the fabric of regulatory decision-making and reimbursement. In England, the National Health Service (NHS) and the National Institute for Health and Care Excellence (NICE) are working on a therapy assessment program to increase access to digitally enabled psychological therapies. In Germany, large insurers are driving adoption. Even France, a relative laggard, has started reimbursing for digital medical devices that fit the DTx definition.

In the U.S., the FDA is promoting a pilot program that may lead to pre-certification for trusted DTx developers whose products will be paired with, or replace, FDA-approved medical treatments. And, the agency recently released a framework for the use of real world evidence (RWE) in clinical studies highlighting the intent to capture more patient-generated data on mobile devices and in-home-use settings.
Well-validated DTx will be a cornerstone of the FDA effort in RWE.

For the same reasons, these novel treatments have caught the eye of payers, whose support will be critical as more products come to market. “What really will be important to the payer community is the collection of real world evidence,” says Susan Cantrell, CEO of the Academy of Managed Care Pharmacy, whose members manage medications for 270 million patients. If all goes well, she says, payers “can be a partner to [DTx] companies as the products come to market, in terms of data collection and strategy for commercialization, and making sure the products get into the hands of patients who need them.”

All signs point to 2019 being a breakthrough year for digital therapeutics. With the market growing 64% CAGR and poised to hit half a billion U.S. dollars by 2021, the industry is approaching an inflection point. In a recent PwC survey, more than half of consumers said they would be somewhat or very likely to try an FDA-approved app or online tool to treat a medical condition, and physicians displayed similar openness to the emerging category.

That said, the business environment is fragmented at this early stage as large and small technology and life sciences companies approach the space with different perspectives and agendas. Partnerships may produce the right blend of skills, but also carry risks, especially for the smaller partner (fig. 1).

Before delving into the challenges DTx startups and biopharma companies face, it’s helpful to understand the confluence of regulatory, technological, social and economic conditions driving estimates of market growth. These include:

- Consistent, supportive signals from the FDA and England’s National Health Service, which already reimburse some digital health solutions
- Rapid technological advances in mobile health, telehealth, health IT and personalized medicine
- Surging consumer interest in self-managed health strategies
- An investment climate that enabled Akili Interactive Labs and Click Therapeutics to raise tens of millions in funding and hundreds of millions in potential milestone payments
- Continued pressure on healthcare systems budgets and the promise of digital therapeutics to deliver efficiencies and more cost-effective care
- Growing consensus around proof points for payers and providers offering DTx solutions to patients
## At A Glance: Trade-offs and Recommendations for Healthcare Stakeholders

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| Large & midsize biopharmaceutical companies considering a partnership | - DTx solutions introduce new business models that are set to disrupt the traditional pharma model  
- DTx solutions provide an opportunity for companies to add value to their portfolios but may necessitate shifts in culture and skill set  
- Cost-effective DTx solutions may soon start winning market share in areas such as depression, addiction, and smoking cessation, as well as obesity and Type II diabetes | - Define strategic partnership criteria to maximize value of portfolios  
- Build internal organizational structures and culture to enable partnerships or develop and deploy DTx solutions  
- Whichever path developers choose, they must be sensitive to consumer concerns around privacy and value |
| DTx solution providers | - DTx solutions are often sub-scale and companies may lack the infrastructure and expertise required to address the plethora of patient, health system, payer and regulatory needs  
- In the past, poor health system engagement, complex reimbursement pathways or convoluted value propositions have hindered wider adoption  
- Pharma companies are building and acquiring DTx capabilities and starting to compete with startups | - Explore optionality in development and commercialization of DTx solutions. For example, partnering with a full-service CRO/CCO that can provide regulatory, market access and marketing expertise may better protect a startup’s intellectual assets than a more traditional alliance  
- Consider integrated development planning at an early stage to avoid pitfalls in approval, reimbursement, and adoption |
### At A Glance: Trade-offs and Recommendations for Healthcare Stakeholders (continued)

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| Payers, including self-funded employer plans | - DTx offer cost-efficiencies and promise improved outcomes but they need to be backed by robust evidence to support claims and demonstrate value  
- Reimbursement pathways in the past have introduced barriers to adoption, especially among public payers | - Encourage collaborative outreach from DTx companies and also begin to educate employers and providers on cost/benefits of DTx, providing the necessary benchmarks  
- Develop a robust evidentiary package to guide developers adopting an FDA-cleared strategic path |
| Hospital systems, ACOs and IDNs | - Providers with large purchasing departments can help spur adoption of DTx  
- DTx solutions must not add overhead or create more work for physicians or health system stakeholders | - Ensure co-development of DTx solutions with health systems  
- Optimize DTx for integration with existing health system workflows  
- Organize forums and provide literature to ensure medical teams and patients understand DTx treatment options |
| Investors | - Backing a startup seeking FDA clearance is different from funding a “digital health” app. Know what you’re looking at and understand the value proposition | - Source cross functional partners to support companies  
- Focus on solutions with peer-reviewed data from randomized trials, while understanding the implications of different FDA classifications—approved, cleared or registered |

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DTx Targets for 2024

Over the next five years, it’s likely the biggest therapeutic targets for DTx will be obesity, diabetes, and other chronic conditions. That includes the opportunity to digitally track and manage health with a holistic approach involving physical activity and eating habits. Another promising application area is disease prevention—especially for respiratory, cardiovascular and CNS conditions. Developers are especially keen on CNS, given the lack of effective treatments for Alzheimer’s disease and Parkinson’s disease and the exit of many large pharma companies from the CNS space. DTx solutions employing cognitive behavioral therapy (CBT), behavioral science, game-style rewards and other strategies for focusing or flexing the brain may help fill the void, assuming developers offer robust clinical evidence to support their assertions.
Anatomy of a Digital Therapeutic

The idea of “software as medical treatment” may seem exotic at first.

But Vincent Hennemand, VP of Strategy, Corporate & Business Development at Akili Interactive, makes the case for similarity. Hennemand says his company’s lead product, a mobile video game to assess and treat ADHD, is being tested in randomized, double-blind, placebo-controlled clinical trials, exactly like a pharmaceutical product—except that the placebo is also a game. Another difference is, the patient’s brain learns and reacts to the DTx treatment, which sends data back to Akili. The product also goes through upgrades, like a phone, a laptop, or a Tesla.

These characteristics “led to funny conversations,” recalls Ed Kliphuis, investment director at M Ventures, one of Akili’s early financial backers. “The first time we approached this, it was ‘okay, do we have a dose response curve? Is there a toxicology profile?’” Kliphuis says. “That led to ‘what is a digital therapeutic and how do we handle it as an investment?’”

As the evidence base grew, the products no longer seemed exotic, and regulators were following the same learning curve. Under the FDA’s latest DTx guidance, if the developer proves the treatment is equivalent or better than the standard of care, upgrades don’t require additional review.

Pear, Akili and other DTx pioneers say the FDA has been tremendously supportive. “They gave us insights into guidelines that were not issued at the time,” says Hennemand. He and others believe the iterative feedback loop with DTx in neural contexts will differentiate these products from less versatile, traditional therapies. That’s one reason for the company’s focus on CNS targets. Over the next five years, Hennemand predicts, DTx will be prescribed for conditions not treatable through other approaches, including cognition impairment linked to inflammatory disorders such as MS, and “chemo-fog” in cancer patients.
“Last Mile” Challenges

Partnerships bridging biopharma and information technology are often in the limelight, and the trend will accelerate.

Last fall, Otsuka Pharmaceutical and Proteus Digital Health expanded their global alliance around one such drug-device hybrid, ABILIFY MYCITE®. Combining aripiprazole (Abilify), an atypical antipsychotic, with a sensor and software, the companies created a smart pill that can track ingestion and transmit the data to patients and doctors via a smartphone app. The FDA approved the drug-ingestion functions of the app in November 2017. The partnership illustrates how large players can provide startups with the infrastructure and resources to support scaling and wider adoption, a challenge plaguing many of the smaller companies and a systemic issue in the fragmented landscape of healthcare solutions.

To be sure, DTx contenders continue to grapple with the “last mile” challenge, including lack of clarity around the reimbursement pathway, and an insufficient analysis of sometimes-conflicting stakeholder needs. All companies in this sector will need to adopt effective engagement strategies and rigorous partnership selection criteria in order to navigate such nuanced issues.
The Empathy Factor

Regulators in the U.S. and Europe have been providing timely, ongoing guidance and encouragement on DTx topics.

Consider the FDA’s Pre-Cert for Software Pilot Program, announced in 2017, as well as the broader Digital Health Innovation Action Plan. One aim is to assess the qualifications of software developers in order to pre-certify initiatives rather than waiting to review a finished app or device. In the test phase, authorities are gathering input from stakeholders on how to regulate pharma companies’ home-grown digital therapeutics, which may be linked to their prescription drug offerings.

But in at least one respect, regulators may need to pay closer heed to consumer sentiments: the threat to privacy from potentially intrusive technology. Last year, Europe enacted the General Data Protection Regulation partly in response to data mining excesses of Facebook, Google and other tech giants. In Europe and the U.S., following waves of revelations about privacy abuse, millions of users deleted their Facebook pages.

Similar risks may arise with DTx. For example, when Apple released its Health Records API in June 2018, it rhapsodized about how “consumers will be able to share medical records from multiple hospitals with their favorite trusted apps, helping them improve their overall health.” It said little about how to prevent dozens, or hundreds, of app developers from exploiting or selling what they learn about customers’ health status.

Considering the scale of the consumer backlash, lawsuits, and public shaming related to the IT privacy debacles, it’s remarkable that the word “privacy” is nowhere to be found on the Apple web page announcing the open API. And while Facebook and Google have acted on some of the recent criticism, smaller companies may need to learn the hard way. As for pharma companies, most are accustomed to operating in a HIPAA-constrained environment and avoiding costly consequences of abusing patient privacy. But even for them DTx is terra incognita.
Data Stewardship

Perhaps the safest path is for healthcare ventures on the digital frontier to put themselves in the patient’s shoes, recognizing that businesses may extract and analyze valuable health data, but that doesn’t confer ownership of the information.

Like pharma companies, DTx players that gather patient data must remember their obligation to use this information in a way that benefits society and not just the bottom line. Ever-growing streams of DTx data will help researchers understand which treatments are effective and for whom—a monumentally important mission. But DTx companies must remain vigilant and conscious of their role as custodians of patient data, not the owners.

The same companies must also show sensitivity toward the heavy administrative burdens that have landed on physicians—a problem technology thus far may have aggravated, not ameliorated. Consider the loathing many doctors feel for health IT systems—an issue chronicled by New Yorker writer Atul Gawande, among others. In a recent survey probing the causes of physician burn-out and stress, the largest cohort—more than one-fifth of respondents—blamed EHRs. This backlash could have been avoided if health IT vendors had put effort into better user-interface design and more physician training on the front end.

Now, imagine the doctor’s plight when consumer health devices owned by scores—or hundreds—of patients in his or her practice are streaming data on heart rate, glucose levels, sleep patterns, and signs of depression. Will beleaguered providers encourage patients to use devices that drastically increase the need to monitor data? It’s possible the only new device physicians will endorse is one that cuts through the cacophony and feeds them only data they deem critical.

For now, it remains to be seen how DTx solutions will improve the signal-to-noise ratio. In fact, in the months since the launch of Apple’s ECG-capable watch, fresh concerns have surfaced about false-positive heart readings. Meanwhile, trailblazing DTx companies appear to be cognizant of these challenges. They are actively pursuing co-development with patients and end users—including HCPs—and optimizing the interventions to deliver real patient value. And they’re taking steps to ensure their products seamlessly integrate into the day-to-day workflow of the healthcare practitioner. But, they must also give thought to additional training and the support needs for sites of care, healthcare practitioners and patients, given the complexity of DTx interventions that integrate a device, software, a drug and a service component.
Gap Analysis

Sensitivity toward doctors, patients and health systems is just one important item on a complicated checklist for DTx players.

Another big question: What does a thriving DTx venture look like and how can companies position themselves for success? In addition to crafting the value proposition, developers must figure out how to structure a commercial model that is win-win for all stakeholders. By now, DTx’s appeal for researchers, product developers and payers is probably self-evident. All these groups are excited by the prospect of continuous real world evidence collection and the resulting dynamic feedback loop.

However, it’s unclear whether commercialization strategies are keeping pace with the enthusiasm. In a recent gap analysis of key market players in DTx, Syneos Health found that a majority of companies recognized the need for randomized clinical trials, but only a handful had managed to formulate a go-to-market strategy or been in touch with payers. Health system engagement was sub-optimal in some instances. The results suggest companies must work harder to educate themselves as well as their target audiences. Cross-functional development is essential—it’s not just about building an evidence package that positions the product for regulatory success or demonstrates cost-effectiveness, but it’s about creating real value for patients that in turn supports not only adoption but also continued utilization.

Confronting these hurdles, many DTx startups hope to rely on resources of Big Pharma partners, as shown by the recent flurry of joint ventures in this space. What smaller players may have overlooked is optionality in alliances. Partnering with a contract research and commercial services organization can be a lean and efficient option for creating an end-to-end evidence story tailored to the smaller firm’s goals and capabilities. Wherever a company stands in the healthcare ecosystem, it should construct the narrative by first identifying and empathizing with the user of the medicine, device or app.

The story a company tells must also be convincing to entities that will pay for the products—insurers, in many cases—and those that will get paid, including both the innovators and the prescribing physicians. Over time, fruitful engagements with one health system or an integrated delivery network will provide proof points and support evidence for the next engagement.
Challenges Amidst Opportunities

Yuri Maricich, Chief Medical Officer and head of clinical development at Pear, applauds the proliferation of DTx in therapeutic areas ranging from obesity and diabetes to neurodegenerative diseases to major depressive disorder. He believes the industry is now at a tipping point.

“We show clinicians the data. It’s robust. Then it’s no longer ‘why should I prescribe this app?’ it’s ‘how should I prescribe this app,’” Maricich says. Because so many doctors are struggling with the lack of good treatment options, he predicts other DTx ventures will have the same experience. “This is not just one or two companies, but a whole sector emerging.”

Yet, many potential stumbling blocks confront DTx innovators, depending on where they fall both inside and outside the traditional biopharma sector. When it comes to market uptake, “the rate limiting factor is just understanding what these tools are, what value they bring, and how to integrate them,” says Megan Coder, Executive Director of the Digital Therapeutics Alliance. “There’s a lot of responsibility on the company side. If you’re claiming to treat an illness with software that’s a big deal.”

While many DTx innovators are beginning to grapple with these near-term obstacles, other potential barriers to success are barely on the radar. It’s imperative to understand potential pitfalls in the area of consumer trust. These include flawed privacy policies, obscure value propositions, pricing missteps, convoluted reimbursement pathways, and failure on the part of many stakeholders to reduce complexity on behalf of the user—meaning patients, physicians, health systems and other stakeholders.
Some experts who come to DTx from the tech industry side recognize the danger of rushing ahead with an engineering solution before fully investigating the customer’s needs. “It’s a perennial problem in tech,” says Andrew Harrison, Head of Business and Corporate Development and Ventures Lead at Verily, the life sciences arm of Google’s parent company, Alphabet: “People sometimes push solutions rather than solving problems.” But he hastens to add that Google makes products two billion people use. When the company develops a healthcare product, he says, “we make sure it fits into the day-to-day life of healthcare professionals. The truth is, you have to innovate differently in healthcare. That’s why Verily exists.” If DTx developers can get out ahead of trust issues as disparate industries converge in this space, traditional medicines and software-based treatments can provide complementary benefits that expand opportunities to keep patients well.

For an early-stage industry, DTx boasts an extraordinary range of innovation engines, from Big Pharma and Big IT down to lone entrepreneurs with game-changing ideas about medicine. In energy, access to capital and pure creative spirit, DTx is already a match for any other sector in healthcare. Regulators in key markets have supported the movement and given it space to breathe. By crafting the optimal value stories, empathizing with key stakeholders and avoiding behaviors that undermine consumer trust, DTx can be everything innovators, patients and providers hope it will be.

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