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THERAPEUTIC DIGEST

DIGITAL THERAPEUTICS

HOW COVID-19 IS RESHAPING THE DIGITAL THERAPEUTICS LANDSCAPE

IN COLLABORATION WITH thinkgen

FEBRUARY 2021

Table of Contents

thinkgen Editorial content provided by ThinkGen (www.think-gen.com)
Written by Kristina Erfe Pines

How COVID-19 is Reshaping the Digital Therapeutics Landscape

In just a few short years, digital therapeutics (DTx) have become an exciting, incredibly competitive new frontier in healthcare. DTx deliver evidence-based therapeutic interventions to patients via software applications, and are meant to prevent, manage, or treat a broad spectrum of physical, mental, and behavioral conditions. Often touted to be just as clinically effective as pharmaceuticals, DTx development costs are significantly less[1] than typical pharmaceuticals, which usually take billions[2] to bring to market. But cost is just one of a growing number of reasons that are attracting more and more people to take DTx seriously.

The market for DTx has been steadily growing.

An independent part of the larger digital-health ecosystem, the market for DTx has been steadily growing. A May 2019 forecast by Juniper Research predicted a 1,000 percent growth trajectory over the next five years to more than $32 billion[3]. However, while the data indicates it's a fertile area in the tedious slow-moving healthcare arena, like all things in health, reaching full market maturity will require convincing healthcare's four big "Ps" — patients, providers, policymakers, and payers.

The COVID-19 pandemic has accelerated our transition and reliance to telemedicine and digital therapeutics. For example, many clinical trial sponsors have adopted telehealth and remote patient monitoring technologies to enable continuity in data collection during the pandemic. Likewise, various mobile medical applications and software functions have been used to support public health surveillance, enable the dissemination of educational materials, and streamline communication for patients and providers. Additionally, regulatory relief from the Centers for Medicare & Medicaid Services (CMS) has enabled clinicians to shift visits to virtual platforms to reduce infection risk to patients.

The Food and Drug Administration (FDA) has issued multiple temporary policies to support the uptake of these tools during the public health emergency[4]. These actions are an extension of the agency's longstanding commitment to advancing regulatory science for DTx, which was articulated in 2017 with the Digital Health Innovation Action Plan and solidified with the creation of the Digital Health Center of Excellence, which was launched in 2020[5,6].

FDA's Regulatory Framework for Digital Therapeutics

When Congress provided FDA with the authority to regulate medical devices in 1976, medical technologies were largely analog[7]. Hardware-based devices differ significantly from software-based

devices in terms of their design, development life cycle, and risk-benefit calculus. As innovators began to develop digital tools to reduce care fragmentation, promote personal wellness and support the diagnosis and treatment of disease, the agency recognized the need to develop regulatory framework that stars current and is attuned to the unique considerations of digital tools[8].

Of note, software functions that do not meet the definition of a medical device in the Food, Drug, and Cosmetic (FD&C) Act are outside of the agency's device regulatory purview. For example, the FDA does not regulate videoconferencing platforms that are used to enhance communication between patients and providers — such as the virtual modalities used for clinical visits during COVID-19 — because they do not meet the device definition. Digital health products that are medical devices, such as mobile medical applications used to diagnose irregularities in the cardiac rhythm, are regulated by FDA according to the level of risk posed to consumers.

To provide momentum for the digital transformation of American medicine, the FDA issued policy guidelines in 2013 and subsequently updated it in 2015 and 2019[9]. Early progress from the FDA's Digital Health Innovation Action Plan was promising and established risk-based policies explaining the FDA's regulatory approach. For example, the agency has focused its oversight on higher-risk mobile medical applications (e.g., those used to diagnose and treat patients), but not on lower-risk digital health products (e.g., those focused solely on promoting wellness)[10].

We need to modernize our regulatory framework so that it matches the kind of innovation we're being asked to evaluate.

As part of the Digital Health Innovation Action Plan, the FDA is also exploring the creation of a Software Pre-Certification program, which is currently in development for software as a pilot medical device[11]. "Our methods for regulating digital health products must recognize the unique and iterative characteristics of these products," says Dr. Scott Gottlieb, former FDA commissioner, in a 2017 press release[12]. "We need to modernize our regulatory framework so that it matches the kind of innovation we're being asked to evaluate." By developing an oversight process and mechanisms that take into account a developer's capabilities streamlined review of the product's analytical and clinical performance, and the products' real-world performance, the agency believes that a regulatory model is envisioned in the Software Pre-Certification Pilot program can be designed to keep pace with digital therapeutic advances and provide a reasonable assurance of safety and effectiveness.

Digital Health Innovation for COVID-19

Several milestones demonstrate how thoughtful regulatory strategies can advance the development of digital health products. For example, the FDA cleared the first-ever digital health therapeutic in 2018 with Novartis and Pear Therapeutics' reSET, the first software-only therapeutic cleared by the FDA. A ninety-day prescription digital therapeutic (PDT), reSET is used for substance-abuse disorders. Its clearance was followed closely by the approval of its sister-product, reSET-O, the first PDT for opioid-abuse disorders. The FDA has cleared several products since then, most recently Akili Interactive's EndeavorRx, a game-based therapeutic for Attention Deficit Hyperactivity Disorder (ADHD)[13,14]. The regulatory decision makes the Boston company's product the first prescription therapy that comes in the form of a video game. "The EndeavorRx device offers a non-drug option for improving symptoms associated with ADHD in children and is an important example of the growing field of digital therapy and digital therapeutics," says Dr. Jeffrey Shuren, director of the FDA's Center for Devices and Radiological Health in a press release last June[15]. "The FDA is committed to providing regulatory pathways to enable patients' timely access to safe and effective innovative digital therapeutics."

> Novartis and Pear Therapeutics' reSET is the first software-only therapeutic cleared by the FDA, which marks the first-ever digital health therapeutic.

To a child playing EndeavorRx, the experience is similar to many quest-type video games. A child controls a character navigating a fantasy world on a hover board. That character must stay on course while steering clear of fire, flying objects, and other distractions or obstacles. The experience is intended to improve a child's ability to pay attention and stay on task. Underpinning the engaging onscreen imagery is Akili's core technology, the Akili Selective Stimulus Management Engine. This technology is designed to target and activate neural systems to improve cognitive functions. The more a child plays, the more attuned the game becomes to his or her behavior. Adaptive algorithms personalize the game experience to each child. Consequently, EndeavorRx constantly challenges players, encouraging them to improve.

The FDA has continued to iterate on its Software Pre-Certification Pilot program, publishing an update on initial lessons in 2020[16]. However, the onset of COVID-19 pandemic has dramatically and rapidly increased the value proposition of digital therapeutics, with unprecedented adoption and utilization of new software tools, and digital platforms by payers and providers to meet the patient needs during the public health emergency. The FDA has sought to expand access to clinically-

appropriate, low-risk digital therapeutic tools during the COVID-19 pandemic by stating its intention not to enforce certain regulatory requirements for some devices.

The FDA issued guidance to temporarily expand patient access to digital health therapeutics for psychiatric disorders.

A clear case of regulatory flexibility is mental health care. Research indicates the pandemic has taken a toll on the well-being of many Americans, with the number of adults reporting symptoms of psychological distress more than tripling in April 2020 compared to April 2018[17]. To address the enhanced mental health burden, the FDA issued guidance to temporarily expand patient access to digital health therapeutics for psychiatric disorders[18]. Under this policy, FDA stated its intention not to object to the distribution and use of such devices (e.g., computerized behavioral therapy, mobile medical applications for mental health) for the duration of the public health emergency without submission of a premarket notification under Section 510(k) of the FD&C Act or compliance with other requirements, such as those for Unique Device Identification.

Likewise, experts are concerned about the health consequences of pandemic-induced interruptions to chronic disease management[19]. Consequently, the FDA issued guidance stating that it does not intend to object to limited modifications to the indications, claims, functionality, hardware, or software of certain non-invasive remote monitoring devices (e.g., blood pressure measurement systems) that are used to support patient monitoring during the public health emergency to help reduce the risk of infection from in-person clinical visits[20].

It is important to emphasize that flexibilities do not compromise the agency's continued prioritization of patient safety and product quality. As noted in the FDA guidance, the temporary policies issued for certain digital health products during the COVID-19 pandemic are limited to select devices with low-risk profiles that can offer meaningful benefit to patients (e.g., DTx for psychiatric disorders). For example, the agency has provided specific examples in its guidance on remote patient monitoring devices to explain when device modifications would not present an undue risk (e.g., changes in parameter display) versus device modifications that do present an undue risk (e.g., functional changes to signal acquisition systems). These actions and scenarios highlight the value of a risk-based approach to regulation, which allows the FDA to be responsive to evolving public health needs by adopting policies for certain low-risk devices, while using agency resources for the evaluation of high-risk products. Of note, several of the software functions relevant for public health officials during the pandemic — such as the use of mobile applications for contact tracing — are not medical devices and therefore do not require FDA device review.

Implications for the Future of Digital Health Regulations

While the pandemic remains ongoing, it is already evident that COVID-19 will have a lasting impact on healthcare delivery. Regulatory flexibilities have been an important enabler of change during the pandemic; However, guidance and policies issued during the pandemic — including those for digital therapeutics — are temporary. FDA intends to rigorously review these temporary policies as part of its Pandemic Recovery and Preparedness Plan, which seeks to identify opportunities for long-term reforms[21,22]. DTx will be a cornerstone of this effort.

The pandemic will provide valuable insights about the utilization of and experience with digital health products.

The pandemic will provide valuable insights about the utilization of and experience with digital health products. Data from payers and developers can provide population-level context about the utilization of technologies such as devices for remote patient monitoring. Meanwhile, feedback from providers and patients can offer experiential insights, form risk tolerance to the compatibility of the user interface. These perspectives can inform how agency officials might adjust the agency's regulatory framework for the digital health products, from determinations of product risk to the proper framework for a future Software Precertification Program.

Research has shown that the uptake of digital health products among elderly Americans has generally lagged due to issues such as the accessibility of product design[23]. However, the pandemic presents an opportunity to accelerate the adoption of digital health technologies among older patients, who may be more likely to now embrace virtual care delivery to minimize their comparatively higher risk for infection. For example, CMS data indicates that the number of Medicare beneficiaries using telehealth services increased from 13,000 to 1.7 million during the COVID-19 pandemic[24]. If similar trends are observed for medical devices (e.g., digital therapeutics, remote patient monitoring technologies,) then the resulting performance data in this population can help harmonize evidence standards for digital health products between the FDA and CMS — a longstanding interagency priority. As regulation of digital health products evolves, payers will need to modernize reimbursement systems to support a world in which the focus of care delivery is increasingly shifted away from the hospital and towards the home. For example, last year CMS issued reimbursement policies for remote patient monitoring (e.g., of physiological parameters such as pulse oximetry). Such services could be integrated into care models such as hospital-at-home programs[25].

The use of digital health tools in clinical trials (e.g., wearables to measure vital signs, mobile applications of measure patient adherence) was already increasing prior to the pandemic, with more than 1100 trials using a connected digital health product in 2018[26]. COVID-19 has provided further momentum for this trend, with pandemic-induced disruptions to trial operations (e.g., delayed patient visits) leading some investigators to adapt study processes using digital tools[27]. To enable continuity in data collection without compromising patient safety, the FDA issued a guidance document outlining the best practices for trial sponsors, including the use of remote patient monitoring and telehealth, when appropriate[28]. Understanding the experience of investigators and study participants with digital health products can help to inform future regulatory guidance, particularly as clinical trials become more decentralized and sponsors work to digitize processes ranging from enrollment to data collection.

Conclusion

The pandemic has accelerated the arrival of the digital era in many aspects of healthcare. From the Canadian startup, BlueDot, the company that rang the bell on a small-scale outbreak in the region of the China's Wuhan province, alerting the world to what is now known as the COVID-19 pandemic[29], to the recent FDA clearance of a mobile sleep app, Nightware[30], created to treat nightmares caused by Post Traumatic Stress Disorder (PTSD). These and other recent milestones in creative and innovative products are paving the way for a new pillar of medicine. The FDA will continue to learn and iterate to advance regulatory science for digital health advancements in accordance with emerging evidence and stakeholder feedback, remaining committed to its goal of supporting patient-centered innovations that are safe and effective.

The FDA will continue to learn and iterate to advance regulatory science for digital health advancements.

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