Recommendations for Regulating Software-Based Medical Treatments: Learning from Therapies for Psychiatric Conditions

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ABSTRACT

Mobile apps and software that claim to treat a diverse set of conditions (including bipolar disorder, depression, and autism) are becoming increasingly popular for their low cost and convenience. While most of these products lack evidence demonstrating their safety or clinical benefits, some developers are submitting clinical studies to the Food and Drug Administration (FDA) in a bid to receive permission to market their products. Some of these efforts have been successful: in September 2017, FDA cleared a mobile medical application for the treatment of substance use disorders, making it the first software-only device that claims to treat a disease to receive FDA marketing permission. This article engages with the question of how FDA should regulate software that claims to treat a disease or condition. The article begins by describing an emerging class of medical devices consisting of mobile apps and other software to treat psychiatric disorders and behavioral or neurodevelopmental conditions ("digital psychiatric therapies"). Digital psychiatric therapies, focused on a subset of conditions, represent the vanguard of the growing trend of "software treatments"—mobile and software applications intended to treat a broad range of diseases and conditions directly. These new technologies raise concerns about safety and effectiveness that the current regulatory framework and pattern of FDA enforcement fails to address systematically. To ensure developer production of clinical studies, this article recommends FDA actively oversee digital psychiatric therapies and other software treatments by setting rigorous safety and effectiveness standards and consistently enforcing them.

INTRODUCTION

Today's world is increasingly digital and electronic with technologies that range from hardware, such as smartphones and wearable devices, to software, such as mobile applications.[1] This trend has sparked a revolution in medical technologies. Over

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[1] According to U.S. Food and Drug Administration (FDA) guidance (discussed below): "a mobile application or "mobile app" is defined as a software application that can be executed (run) on a mobile platform (i.e., a handheld commercial off-the-shelf computing platform, with or without wireless connectivity), or a web-based software application that is tailored to a mobile platform but is executed on a

325,000 mobile health applications are currently available through major app stores.[2] Forecasts for 2020 estimate that global revenue from mobile health app-related services will be $31 billion and mobile health apps will have 551 million monthly users.[3] Available technologies perform a variety of functions.[4] For example, many apps encourage and reinforce behavioral change (e.g., helping users stop smoking by tracking the benefits of quitting[5]). Other technologies transform consumer mobile devices into diagnostic devices (e.g., enabling a tablet or smartphone to function as an ultrasound machine[6]).

Another group of mobile and software applications seeks to treat specific diseases and conditions rather than merely serving as a behavior reinforcement or diagnostic tool ("software treatments").[7] Software to treat psychiatric and behavioral conditions in particular has received significant attention from the media and investors.[8] This subset of mobile applications, software intended to treat or mitigate psychiatric disorders and behavioral or neurodevelopmental conditions ("digital psychiatric therapies"[9]), include software that uses virtual reality and real-time therapeutic interventions to treat conditions ranging from post-traumatic stress disorder (PTSD) and memory loss to attention deficit hyperactivity disorder (ADHD) and autism. Building off trends in other areas of health,[10] many of these therapies take the form of games.

This article primarily focuses on digital psychiatric therapies because the market for these treatments is the most developed. Software cannot plausibly claim to treat

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server." FOOD & DRUG ADMIN., MOBILE MEDICAL APPLICATIONS: GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF 7 (2015) [hereinafter MMA GUIDANCE], http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm263366.pdf [https://perma.cc/QU4W-ED5M].

2 RESEARCH2GUIDANCE, MHEALTH APP DEVELOPER ECONOMICS 2017, at 9 (2017).

3 RESEARCH2GUIDANCE, MHEALTH APP DEVELOPER ECONOMICS 2016, at 9 (2016); *see also* Laurence Goasduff, *10 Wearable Technologies and Capabilities That Should Not Be Ignored*, GARTNER, (Aug. 10, 2016), http://www.gartner.com/smarterwithgartner/10-wearable-technologies-and-capabilities-that-should-not-be-ignored/ [https://perma.cc/DNQ7-4SRT] (estimating wearable technology sales of 275 million units in 2016 and 477 million units worth $67.1 billion in 2020).

4 For a taxonomy of mobile health technologies, see Nathan Cortez, *The Mobile Health Revolution?*, 47 U.C. DAVIS L. REV. 1173, 1181–90 (2014).

5 *E.g.*, SMOKE FREE, http://smokefreeapp.com [https://perma.cc/9SW3-FH5R] (last visited Sept. 26, 2017).

6 *E.g.*, MOBISANTE, http://www.mobisante.com [https://perma.cc/R795-MKNT] (last visited Sept. 26, 2017).

7 These treatments have their own distinct medical purpose and are therefore different from software that controls or operates another medical device such as an infusion pump or pacemaker.

8 *See, e.g.*, Cade Metz, *A New Way for Therapists to Get Inside Heads: Virtual Reality*, N.Y. TIMES (July 30, 2017), https://www.nytimes.com/2017/07/30/technology/virtual-reality-limbix-mental-health.html [https://perma.cc/626L-AG7F].

9 For the purposes of this paper, I define digital psychiatric therapies as software and wearables that treat or mitigate the symptoms of psychiatric or behavioral (as opposed to purely physical) conditions through means other than behavior reinforcement (e.g., symptom tracking). This software is distinct from telehealth, which connects patients to treatment (usually medical professionals) through digital and/or online means.

10 *See* Carleen Hawn, *Games for Health: The Latest Tool In The Medical Care Arsenal*, 28 HEALTH AFF. w842, w843 (2009) ("Research is beginning to show that the [exercise] games are far more than just entertainment and truly can lead to healthier behavior and better health.").

the vast majority of medical conditions or replace existing treatments. It is relatively easy to imagine software replacing a psychiatric therapy session whereas software alone cannot serve as an effective hip replacement or oncologic treatment. Because digital psychiatric therapies can serve a therapeutic function that software treatments for other conditions and diseases cannot, it is unsurprising that they have gained prominence most quickly. It was also predictable that FDA's first clearance for a software treatment, Pear Therapeutics' reSET to help treat substance use disorders (SUD), was a digital psychiatric therapy.[11] However, companies developing software treatments may claim to treat a variety of medical conditions, a function for software that is under-studied in the legal literature.[12] In the future, software treatments for physical conditions may be more prevalent, and this article uses the discussion of digital psychiatric therapies as a starting point for a broader regulatory analysis.

If digital psychiatric therapies are effective, they hold significant promise to address mental health, particularly among patients who lack access to treatment, and to reduce health care costs. Estimates suggest almost one-third of people in high-income countries develop a mental illness in their lifetime,[13] and there is a universally large treatment gap for psychiatric disorders.[14] One meta-analysis of 203 studies conducted in 29 countries found people with mental disorders have a mortality rate more than two times higher than the comparison population, and eight million deaths worldwide are attributable to mental disorders each year.[15] Mobile health solutions can increase access, particularly for patients in areas that are more remote or lack health care professionals. Because digital solutions are less costly than individual treatment by a mental health professional, digital psychiatric therapies offer an opportunity to control rising health care costs.[16] By expanding access to treatment or supporting existing treatments, these applications might contribute to closing the treatment gap around the world.

However, software developers are often unfamiliar with FDA regulation.[17] When developers do consider FDA's role, the uncertainty that surrounds existing regulations

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[11] *FDA Permits Marketing of Mobile Medical Application for Substance Use Disorder*, FOOD & DRUG ADMIN. (Sept. 14, 2017), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm576087.htm [https://perma.cc/P3AY-4F6T].

[12] Professor Cortez's hierarchy, for example, includes six types of mobile health apps that he terms: (1) connectors; (2) replicators; (3) automators and customizers; (4) informers and educators; (5) administrators; and (6) loggers and trackers. Cortez, *supra* note 4. Although some of these app types might deliver therapy directly, Professor Cortez does not characterize them on that basis. Moreover, discussions of mobile health apps in this area have primarily focused on software's role as a diagnostic tool. This perspective envisions software that provides customized "patient-specific diagnosis, or treatment recommendations," which would be administered through other means. MMA GUIDANCE, *supra* note 1, at 15. Meanwhile, scholars and practitioners have begun to recognize the utility of mental health apps in supporting and providing care. *See, e.g.*, Justin Marley & Saeed Farooq, *Mobile Telephone Apps in Mental Health Practice: Uses, Opportunities and Challenges*, 39 BJPSYCH BULL. 288, 289 (2015).

[13] Zachary Steel et al., The Global Prevalence of Common Mental Disorders: A Systematic Review and Meta-Analysis 1980–2013, 43 INT'L J. EPIDEMIOLOGY 476, 485 (2014).

[14] Robert Kohn et al., *The Treatment Gap in Mental Health Care*, 82 BULL. WORLD HEALTH ORG. 858 (2004).

[15] Elizabeth Reisinger Walker et al., Mortality in Mental Disorders and Global Disease Burden Implications: A Systematic Review Meta-analysis, 72 JAMA PSYCHIATRY 334, 339 (2015).

[16] *See* Cortez, *supra* note 4, at 1195–97.

[17] Nathan Cortez, *Analog Agency in a Digital World*, *in* FDA IN THE TWENTY-FIRST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES 438, 450 (Holly Fernandez Lynch & I.

may create barriers to development.[18] Companies may be reluctant to invest significant resources in a particular area if those investments will become moot due to a shift in regulation.[19] Companies have responded either by embracing FDA's regulation of their products or attempting to avoid regulation. Multiple companies have products that they anticipate will be regulated as medical devices and have announced they will eventually file for marketing clearance or approval from FDA. Akili Interactive Labs is developing the game "Project: EVO" to mitigate ADHD symptoms in kids.[20] In addition to its reSET product, Pear Therapeutics is developing a suite of "digital therapeutics" software, often for use in conjunction with pharmaceutical treatment.[21] Other companies, particularly those focused on "brain games," have eschewed FDA involvement and have chosen to make general rather than condition-specific claims. For example, some companies, such as Lumosity[22] and Cogmed,[23] claim to provide "brain training" or improve "working memory," a term used to describe the brain function that addresses short-term tasks requiring both storage and processing,[24] rather than explicitly treating memory loss. However, there is limited evidence these types of products improve working memory or treat other conditions effectively.[25]

Glenn Cohen eds., 2015) ("[L]arge modern software device manufacturers are well acquainted with FDA requirements. But the latest generation of software developers for mobile devices seems naïve to them.").

[18] Lesley McClurg, *Getting FDA Approval is Hot Topic at Neurogaming Conference*, KQED SCIENCE: FUTURE OF YOU (May 20, 2016), http://ww2.kqed.org/futureofyou/2016/05/20/to-fda-or-not-to-fda-is-hot-topic-at-neurogaming-conference/ [https://perma.cc/EP4H-2SD9].

[19] *See* Letter from Access Integrity et al. to Congress (Oct. 7, 2014), http://www.healthitnow.org/wp-content/uploads/2014/10/Multi-Group-FDASIA-Letter-to-Congress.pdf [https://perma.cc/SMD4-AFE2] ("The potential cost and delay created by current regulatory uncertainty may further deter software and system developers from creating products that have the ability to greatly benefit patients.").

[20] AKILI, http://www.akiliinteractive.com [https://perma.cc/F49N-X8TF] (last visited Sept. 26, 2017).

[21] PEAR THERAPEUTICS, https://peartherapeutics.com [https://perma.cc/87HV-C8DS] (last visited Sept. 26, 2017).

[22] LUMOSITY, https://www.lumosity.com [https://perma.cc/XMP5-KZUK] (last visited Sept. 26, 2017).

[23] Pearson Education, COGMED WORKING MEMORY TRAINING, http://www.cogmed.com [https://perma.cc/3LTT-RAKD] (last visited Sept. 26, 2017).

[24] Nelson Cowan, *What Are the Differences Between Long-Term, Short-Term, and Working Memory?*, 169 PROGRESS BRAIN RES. 323, 325 (2008); *see also About Working Memory*, COGMED WORKING MEMORY TRAINING, http://www.cogmed.com/about-working-memory [https://perma.cc/8MVE-AZ2P] (last visited Sept. 26, 2017) ("Working memory is the cognitive function responsible for keeping information online, manipulating it, and using it in your thinking. It is the way that you delegate the things you encounter to the parts of your brain that can take action.").

[25] Monica Melby-Lervåg & Charles Hulme, *Is Working Memory Training Effective? A Meta-Analytic Review*, 49 DEVELOPMENTAL PSYCHOLOGY 270, 282 (2013) (finding that effects of working memory training are not generalizable to cognitive performance); Thomas S. Redick et al., *No Evidence of Intelligence Improvement After Working Memory Training: A Randomized, Placebo-Controlled Study*, 142 J. EXPERIMENTAL PSYCHOLOGY 359, 377 (2013) (finding improvements in visual search tasks from working memory training did not transfer to cognitive ability tests); *see also A Consensus on the Brain Training Industry from the Scientific Community*, STAN. CTR. ON LONGEVITY (Oct. 20, 2014), http://longevity3.stanford.edu/blog/2014/10/15/the-consensus-on-the-brain-training-industry-from-the-scientific-community/ [https://perma.cc/FF2P-NGCU].

Since the science of apps for mental health is just beginning to emerge,[26] it is unclear how safe and effective any of these approaches are as therapy for psychiatric conditions, raising the question of whether and how they should be regulated. FDA is in a challenging position. FDA is a public health agency with a mandate to prevent unsafe and ineffective therapies from reaching the market and FDA regulation shapes innovation in the medical arena by setting the standards drug and device manufacturers must meet to market their products.[27] Some argue that FDA regulation intended to protect patients unnecessarily dampens innovation and prevents patients from accessing potentially helpful therapies.[28] This general critique has been levied in the context of FDA regulation of emerging health technologies.[29] However, other scholars have noted the role FDA regulation plays in incentivizing the production of valuable information about regulated products.[30] Potential regulated parties, including companies developing mobile health technologies, have also recognized the role that clear and robust FDA regulation plays in constituting an emerging market.[31]

Recognizing the promise of software treatments will require them to be safe and effective. However, patients and physicians have difficulty evaluating the merits of mobile health apps,[32] raising the concern that patients with psychiatric conditions will

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[26] Emily Anthes, *Pocket Psychiatry*, 532 NATURE 20, 21–22 (2016), http://www.nature.com/news/mental-health-there-s-an-app-for-that-1.19694/ [https://perma.cc/T9X4-KM66] (expressing concerns about the lack of trials and the scientific rigor of trials conducted).

[27] *What does FDA do?*, FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194877.htm [https://perma.cc/3NMZ-UW2U] (last visited Sept. 26, 2016) (FDA "[p]rotect[s] the public health by . . . ensuring that human and veterinary drugs, and vaccines and other biological products and medical devices intended for human use are safe and effective"); s*ee also* DANIEL CARPENTER, REPUTATION AND POWER (2010); PHILIP J. HILTS, PROTECTING AMERICA'S HEALTH: THE FDA, BUSINESS, AND ONE HUNDRED YEARS OF REGULATION (2003).

[28] *See, e.g.*, Abigail Alliance v. Von Eschenbach, 445 F.3d 470, 470 (D.C. Cir. 2006) (holding FDA's denial of investigational drugs to terminally-ill adult patients violates a due process right), *vacated*, 495 F.3d 695 (D.C. Cir. 2007) (en banc).

[29] *E.g.*, Deb Fischer & Angus King, *FDA's Slow Process Hurts Innovation: Column*, USA TODAY (Feb. 15, 2014), http://www.usatoday.com/story/opinion/2014/02/15/fischer-king-health-information-technology/5464693/ [https://perma.cc/B9ZL-ZECH] ("Companies . . . are left on uncertain footing given the FDA's regulatory discretion. Such heavy-handed moves have caused legitimate concern that the FDA could slow down the development of low-risk health technology, including mobile-wellness applications and electronic health records.").

[30] *E.g.*, Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. TECH. L. REV. 345, 370 ("The FDA uses its powers as a market gatekeeper and as a censor of marketing claims not just to protect patients from untoward risks of harm, but also to motivate drug sponsors to generate valuable information about their drugs."); *see also* Cortez, *supra* note 17, at 448 ("Software devices are in great need of more predictable, tailored oversight . . . . The market risks being flooded by apps that are ineffective or unsafe, which can undermine consumer confidence.") (citation omitted).

[31] Letter from Bradley Merrill Thompson on behalf of mHealth Regulatory Coalition to Senators Tom Harkin & Michael B. Enzi, Committee on Health, Education, Labor and Pensions (May 17, 2012), http://mhealthregulatorycoalition.org/wp-content/uploads/2010/06/MRC-Letter-to-Senate-HELP-Committee-on-Proposed-Moratorium-FINAL.pdf [https://perma.cc/A6CK-F8WU] (opposing an amendment to a FDA user fee bill that would have prohibited FDA from finalizing its Draft Guidance for eighteen months); *see also* Nathan Cortez, *Regulating Disruptive Innovation*, 129 BERKELEY TECH. L.J. 175, 204 (2014) ("[E]arly interventions can benefit both regulated industry and regulatory beneficiaries.").

[32] Health app overload, an inability to deal with the large supply of apps, makes it more difficult for health professionals and patients to find the right apps for them. Lex van Velsen et al., *Why Mobile Health App Overload Drives Us Crazy, and How to Restore the Sanity*, 13 BMC MED. INFORMATICS & DECISION MAKING 23 (2013). For example, one study reviewing 82 consumer-focused apps for bipolar disorder found that average user ratings were not significantly correlated with comprehensiveness of psychoeducation

be relying on "digital snake oil."[33] The regulatory approach to digital psychiatric therapies and other early software treatments will shape industry action and the government's future set of regulatory options. The stakes for FDA in this area are high and the agency should act quickly: the initial rules of the game will be difficult to change in the future as stakeholders gain an interest in maintaining the status quo.[34]

This article explores a critical question: How should FDA respond to ensure the development of effective software treatments? Part I describes the emergence of digital psychiatric therapies and provides an overview of the market for these new technologies. Part II examines FDA's current regulatory scheme for medical software and raises questions about how FDA will apply it to digital psychiatric therapies and other software treatments. Part II also describes the roles other stakeholders have played in regulating this market. Part III identifies the specific concerns that the innovation of digital psychiatric therapies and other software treatments raise and discuss how the regulatory scheme fails to address them. Part IV advocates for a more active FDA role in regulating software treatments and offers recommendations to help ensure the safety and effectiveness of digital psychiatric therapies and other software-based medical treatments available to consumers.

I. THE EMERGENCE OF DIGITAL PSYCHIATRIC THERAPIES

Digital psychiatric therapies are a growing part of the digital health ecosystem and present a variety of approaches to mental health care for different populations and different conditions. Initial medical research in this field is limited, however, and may require federal regulation to stimulate rigorous study.

A. The Digital Psychiatric Therapies Landscape

Digital psychiatric therapies are a relatively small but growing segment of the rapidly expanding mobile health market. Given the rapid pace of software development, there is no definitive picture of the digital psychiatric therapy market or the mobile health market generally. Cognitive-behavioral therapy (CBT) interventions are among the most common digital psychiatric therapies; one study identified 477 commercially available apps focused on cognitive-behavioral interventions.[35] Digital versions of forms of psychotherapy other than CBT, as well as more innovative

information and information quality. The study also found no significant difference in information comprehensiveness or quality between free and paid apps. Jennifer Nicholas et al., *Mobile Apps for Bipolar Disorder: A Systematic Review of Features and Content Quality*, 17 J. MED. INTERNET RES. e198, 8–9 (2015).

[33] Press Release, AMA CEO Outlines Digital Challenges, Opportunities Facing Medicine, Am. Med. Ass'n (June 11, 2016), https://www.ama-assn.org/ama-ceo-outlines-digital-challenges-opportunities-facing-medicine [https://perma.cc/LSX5-UWCB].

[34] Cortez, *supra* note 31, at 204 ("Early interventions may also benefit from a more objective regulatory atmosphere, before parties become entrenched and adversarial."); David A. Super, *Against Flexibility*, 96 CORNELL L. REV. 1375, 1378 (citing JOHN RAWLS, A THEORY OF JUSTICE 136–37 (1971)) ("[P]recommitment in policymaking is appealing in large part because it is *not* well-informed and can serve as a sort of 'veil of ignorance' to filter out some self-serving biases.").

[35] John Torous et al., *Cognitive Behavioral Mobile Applications: Clinical Studies, Marketplace Overview, and Research Agenda*, 24 COGNITIVE & BEHAV. PRAC. 215, 215 (2017).

treatments, are available as well.[36] However, relative to other types of apps—such as educational, screening, monitoring, and community support apps—treatment apps are relatively rare. One review of consumer-focused apps related to bipolar disorder (BD) found only one treatment app among the 82 apps reviewed.[37] Commercially available apps are often free, though some apps cost money or have premium features that users can purchase.[38] More complex therapy modalities are likely to be significantly more expensive.[39] Although many digital psychiatric therapies are under study and are not available to the public commercially,[40] the market for these apps is likely to continue to grow.

The demand for these products is high and industry is investing significant capital in digital psychiatric therapies. Large pharmaceutical and biotech companies such as Amgen, Merck, Novartis, Pfizer, and Shire are already collaborating with or investing in companies developing digital psychiatric therapies.[41] Mobile health generally has attracted significant investment,[42] and some developers have raised funding rounds of tens of millions of dollars from investors, including traditional venture capital firms.[43]

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[36] Christopher G. Fairburn & Vikram Patel, *The Impact of Digital Technology on Psychological Treatments and Their Dissemination*, 88 BEHAV. RES. & THERAPY 19, 19–20 (2017).

[37] Nicholas et al., *supra* note 32, at 9.

[38] *E.g.*, Anna Huguet et al., *A Systematic Review of Cognitive Behavioral Therapy and Behavioral Activation Apps for Depression*, 11 PLOS ONE e0154248, at 7 (2016) ("The cost of these CBT/BA apps ranged from $0.00 to $8.99."); Nicholas et al., *supra* note 32, at 7 ("49 apps were free, and the median cost of paid apps was AU$1.70, with a minimum price of AU$0.99 and a maximum of AU$16.99 (mean AU$3.05).").

[39] *See* Joe Donnelly, *How Virtual Reality Is Revolutionizing Clinical Therapy and Treatment Rehabilitation*, VICE (Sept. 22, 2016, 11:50 AM), https://www.vice.com/en_us/article/how-virtual-reality-is-revolutionising-clinical-therapy-and-treatment-rehabilitation-110 [https://perma.cc/J2HP-UM6S] (reporting that the Canadian government purchased the latest version of a virtual reality exposure therapy for PTSD at a cost of $17,000). The need to recoup some therapies' high costs of development will likely lead to developers charging more for their products. Given the prices for digital therapies in other areas of health, successful digital psychiatric therapies may charge significantly more than currently available apps. *See* Christina Farr, *Can "Digital Therapeutics" Be as Good as Drugs?*, MIT TECH. REV. (Apr. 7, 2017), https://www.technologyreview.com/s/604053/can-digital-therapeutics-be-as-good-as-drugs/ [https://perma.cc/JM93-LCX5] ("Omada Health in 2016 again broke ground when Medicare agreed to reimburse the cost of its digital diabetes prevention program. The company didn't say how much it bills employers and insurance plans, but it would charge a self-paying customer $140 a month for the first four, then $20 per month.").

[40] *See* Torous et al., *supra* note 35, at 220–21 (finding that only three of the nine clinically studied cognitive-behavioral interventions were commercially available).

[41] Rebecca Robbins, *Inside the Push to Get Doctors to Prescribe Video Games*, STAT (Nov. 5, 2015), https://www.statnews.com/2015/11/05/video-game-developers-covet-new-market-patients/ [https://perma.cc/C2BH-L4V2]; AKILI, *supra* note 20 (listing Pfizer, Shire, Merck Ventures and Amgen among the company's partners); PEAR THERAPEUTICS, *supra* note 21 (listing Novartis among the company's partners).

[42] *See* Steven R. Steinhubl et al., *The Emerging Field of Mobile Health*, 7 SCI. TRANSLATIONAL MED. 283rv3 (2015) (estimating $1 billion of venture capital in mobile health funding annually); *see also* RESEARCH2GUIDANCE, *supra* note 2, at 12–13 (estimating total global investment in digital health start-ups at $5.4 billion in 2016).

[43] Julie DiCarlo, Digital Medicine Company Akili Interactive Labs Raises $30.5 Million to Advance Product Development and Build Commercial Infrastructure, BUSINESS WIRE (Jan. 22, 2016, 2:00 AM), http://www.businesswire.com/news/home/20160121006550/en/Digital-Medicine-Company-Akili-Interactive-Labs-Raises [https://perma.cc/9TWA-MN9A]; Joseph Keenan, Merck, Amgen Bump up Series B to $42.4M for Akili, FIERCEBIOTECH (July 20, 2016, 10:06 AM), http://www.fiercebiotech.com/medical-devices/akili-adds-11-9m-from-merck-and-amgen-to-push-its-series-b-total-42-4m [https://perma.cc

Government and nonprofit organizations have also contributed capital in the form of grants to study these emerging technologies.[44] Relative to the billions of dollars spent on drug development annually, these investments in digital psychiatric therapies are small, but reflect the commercial promise of these products.[45] To capitalize on consumers' demand for these products, some companies developing new technologies are even relying on popular crowdfunding platforms to raise money for their products.[46] These companies sometimes offer the products for sale through crowdfunding websites prior to FDA clearance.[47] This trend has not spread widely to digital psychiatric therapies, but, as interest in them grows, smaller companies may look for new ways to raise capital.

Digital psychiatric therapies treat a wide range of different conditions through a variety of treatment modalities.[48] Specific treatment modalities include CBT,[49] videogames,[50] virtual reality exposure therapy,[51] and digital therapies combined with traditional pharmaceuticals.[52] These modalities can range from relatively simple to quite complex. One app for smartphone and tablets that utilizes CBT to treat depression presents six lessons in a format similar to a comic book and follows the story of a fictional character who learns to manage her depressive symptoms.[53] At the end of each lesson, the app assigns the user "relevant homework activities."[54] The user is also able to access "[a]dditional resources, such as information on assertiveness skills and sleep hygiene, and stories from previous participant's [sic] experiences."[55]

/4Q7W-TL4Y]; Aditi Pai, Pear Therapeutics Raises $20M for Digital Combination Interventions, Starting with Substance Use Disorders, MOBIHEALTHNEWS (Feb. 3, 2016), http://www.mobihealthnews.com /content/pear-therapeutics-raises-20m-digital-combination-interventions-starting-substance-use [https://perma.cc/4X64-YDH5].

[44] Robbins, *supra* note 41.

[45] *Id*.

[46] Rebecca Robbins, *Crowdfunding of Medical Devices Raises Money—and Questions*, BOSTON GLOBE (Sept. 8, 2015), https://www.bostonglobe.com/business/2015/09/07/crowdfunding-medical-devices-raises-money-online-questions-the-fda-hasn-reviewed-these-medical-devices-yet-but-you-can-buy-them/RoVuxMgfefPufzuEKYzA4I/story.html [https://perma.cc/N9HC-CLEN].

[47] *Id.*

[48] *See* Tara Donker et al., *Smartphones for Smarter Delivery of Mental Health Programs: A Systematic Review*, 15 J. MED. INTERNET RES. e247, 2 (2013) (defining the mental health app market to include conditions such as depression, anxiety, substance abuse, suicidal behavior, psychotic disorders and stress in groups such as children, adolescents, adults, and the elderly).

[49] Torous et al., *supra* note 35.

[50] *E.g.*, AKILI, *supra* note 20; BIOSTREAM TECH., http://www.biostreamtech.com/ [https://perma.cc /L74F-YPHK] (last visited Sept. 26, 2017) (developing a video game therapy to help children with autism spectrum disorder improve social skills).

[51] Alex Senson, *Virtual Reality Therapy: Treating The Global Mental Health Crisis*, TECHCRUNCH, Jan. 6, 2016, https://techcrunch.com/2016/01/06/virtual-reality-therapy-treating-the-global-mental-health-crisis/ [https://perma.cc/8QJ8-X7TB].

[52] PEAR THERAPEUTICS, *supra* note 21.

[53] Sarah Watts et al., CBT for Depression: A Pilot RCT Comparing Mobile Phone vs. Computer, 13 BMC PSYCHIATRY 49, 4 (2013).

[54] *Id.*

[55] *Id.*

Another set of apps uses videogame-like formats to engage users and treat their conditions.[56] One game under study for ADHD involves two components. One "requires the subject to navigate a character through a game-like space, while collecting objects, in a fixed period of time"; a second "requires the subject to spell as many words as possible, by connecting letters in a game-like grid, in a fixed period of time."[57] These videogame-like products emphasize the importance of entertainment with elements such as "animations, music, levels, [and] power-ups."[58] The theory is that "therapies are more effective when patients stick with them" and video games are more likely to appeal to patients (and encourage patients to keep playing through challenges) by being fun.[59]

These devices can also be quite specific in their use and may require professional supervision. Pear Therapeutics' reCALL uses a virtual reality visor in combination with traditional pharmaceuticals to treat veterans with PTSD and combat-related depression.[60] A similar virtual reality device operates by gradually immersing patients with PTSD into multi-sensory and interactive virtual environments that represent their traumatic experiences.[61] Patients often find it challenging to imagine their traumatic experiences, so virtual reality can help them relive painful events and thereby process the emotions associated with the traumatic experiences in a controlled manner.[62]

The variety, specificity, and number of digital psychiatric therapies make it difficult for regulators to impose a single framework or clearance process. These characteristics of the market also make it extremely complex for patients and health care professionals to compare the effectiveness of different software treatments, even when targeted for the same population and condition.[63]

B. The Limitations of Existing Clinical Research

The science of digital psychiatric therapies is in its infancy in part because many companies are foregoing the cost of rigorously studying their devices.[64] Only a few developers have initiated and registered clinical trials for their devices.[65] A recent

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[56] *E.g.*, AKILI, *supra* note 20; BIOSTREAM TECH., *supra* note 50.

[57] Akili Interactive Labs, *Software Treatment for Actively Reducing Severity of ADHD (STARS-ADHD)*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT02674633 [https://perma.cc/KLQ8-FZX2] (last updated Aug. 3, 2017).

[58] BIOSTREAM TECH., *supra* note 50.

[59] *Id.*

[60] *reCALL*, PEAR THERAPEUTICS, https://peartherapeutics.com/ptsd/ [https://perma.cc/YK44-YSD9] (last visited Sept. 26, 2017) ("VRET is a clinically validated treatment that can decrease anxiety and depression, and lower symptom severity of PTSD.").

[61] *Bravemind*, U.S. CAL. INST. CREATIVE TECH., http://medvr.ict.usc.edu/projects/bravemind/ [https://perma.cc/ZEF6-Y752] (last visited Sept. 26, 2017) ("Bravemind is a clinical, interactive, virtual reality (VR) based exposure therapy tool being used to assess and treat post traumatic stress disorder (PTSD).").

[62] *Id.*

[63] *See* Van Velsen et al., *supra* note 32.

[64] Anthes, *supra* note 26.

[65] *E.g.*, Akili Interactive Labs, *supra* note 57 (studying videogame-like digital therapy for children diagnosed with ADHD); Dartmouth-Hitchcock Med. Ctr., *Comparing Mobile Health (mHealth) and Clinic-Based Self-Management Interventions for Serious Mental Illness*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT02421965 [https://perma.cc/45VK-3SC9] (last updated May 24, 2017); Emory Univ., *BraveMind: Advancing the Virtual Iraq/Afghanistan PTSD Exposure Therapy*,

study identified just eight published clinical studies of apps with mental health interventions, and most of these studies were of low quality without rigorous assessments of the apps' efficacy.[66] Without detailed clinical data, it is also difficult to make judgments regarding digital psychiatric therapies' cost-effectiveness.[67] Some software developers may be unaware of FDA's expectations, while others argue that FDA does not impose a requirement but instead offers the choice to engage in clinical study. Companies often view themselves as making a business decision and pursue rigorous clinical trials only when the studies will give their products a competitive advantage worth the time and expense.[68]

This lack of study is especially alarming because digital psychiatric therapies often do not conform to existing standards of care for the specific conditions they claim to treat. One study evaluated 117 apps identified from the scientific literature and the commercial market as intended to treat depression.[69] The researchers found no studies demonstrating the effectiveness or efficacy of these apps.[70] Moreover, although there is strong evidence for the effectiveness of CBT or behavioral activation (BA) in treating depression, only 12 of the 117 apps offered support in line with CBT or BA, and their adherence to CBT and BA principles was inconsistent.[71] Given the lack of rigorous evidence and the limited adherence to the CBT and BA models, the authors of the study concluded that the utility of available apps to treat depression is questionable.[72] Although the treatment app identified in the study of apps for BD offered a CBT intervention, the intervention's design was not specific to BD and "the source or evidence base of the CBT presented in the app was not referenced."[73]

Recognizing the difficulties in evaluating digital therapeutics such as digital psychiatric therapies, some commentators have proposed self-regulation schemes for industry.[74] One proposal suggests a certification or third-party review system that

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CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT02246972 [https://perma.cc/YPW4-VNGL] (last updated Aug. 9, 2017); Pfizer, *A Study To Evaluate the Difference in iPad-Based Cognitive Video Game (Akili Interactive's Project: EVO) Performance in Amyloid-Positive Versus Amyloid-Negative Healthy Elderly Volunteers*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT02265718 [https://perma.cc/5HSB-RJDF] (last updated July 26, 2016).

66 The study authors conducted a comprehensive literature search and examined 5464 abstracts. They only included those studies that examined the effects of mental health apps delivered on mobile devices with a pre- and post-test assessment or a comparison group. Donker et al., *supra* note 48.

67 *Id.* at 9 ("The cost-effectiveness and cost-utility of mHealth, compared to standard care or Internet-based treatment, requires further examination.").

68 *See* McClurg, *supra* note 18 ("'I think this is going to play out a lot like the drug versus supplement route,' says Corey McCann, CEO of Pear Therapeutics. 'There will be some products that have some data and there will probably be a premium price that is associated with them. Physicians will be comfortable using them, and payers will feel comfortable reimbursing for them. And you'll have other products that are not backed by data, and that's the more supplement approach or direct-to-consumer approach.'").

69 Huguet et al., *supra* note 38.

70 *Id.* at 7–8.

71 *Id.* at 7.

72 *Id.* at 14.

73 Nicholas et al., *supra* note 32, at 9.

74 *E.g.*, Urs-Vito Albrecht, *Transparency of Health-Apps for Trust and Decision Making*, 15 J. MED. INTERNET RES. e277 (2013); Steven Chan et al., *Towards a Framework for Evaluating Mobile Mental Health Apps*, 21 TELEMEDICINE & E-HEALTH 1038 (2015); Maurits Graafland et al., *How to Systematically*

evaluates apps along a variety of criteria.[75] Another proposal suggests creating standardized frameworks for mobile health apps to promote uniformity and easy comparison.[76] However, previous third-party certification efforts have not been successful.[77] Moreover, major medical societies have been slow to formulate guidelines,[78] and there is little incentive for developers themselves to generate this information since negative results have the potential to undercut sales.[79] Given the limited prospects for self-regulation, government actors are in the best position to address digital psychiatric therapies.

In summary, commercially available apps in this area lack rigorous evidence that they effectively treat patients. Without the intervention of the federal government, it seems unlikely that digital psychiatric therapy developers will conduct clinical trials to ensure the safety and effectiveness of their products.

II. REGULATION OF DIGITAL PSYCHIATRIC THERAPIES IN THE UNITED STATES.

Like all executive agencies created by Congress, FDA has a regulatory scheme based upon legislative delegation. Consistent with FDA interpretation of its jurisdiction over mobile applications, FDA has the power to regulate digital psychiatric therapies as medical devices if they meet certain statutory criteria. However, the administrative actions that build upon the statute (including FDA regulations and guidance) are less clear when applied to digital psychiatric therapies and other software-based medical treatments. Under the existing regulatory framework, it is difficult to determine whether a medical app is a device and, if so, what is required for FDA to authorize marketing for that device. Moreover, FDA's existing guidance fails to distinguish digital psychiatric therapies and other software-based medical treatments from mobile applications that serve other purposes, leaving open the question of whether FDA will exercise enforcement discretion over software treatments. Other government actors, such as Congress, Federal Trade Commission (FTC), and state attorneys general, have also exercised authority over digital psychiatric therapies, further complicating the regulatory outlook.

Assess Serious Games Applied to Health Care, 2 J. MED. INTERNET RES. SERIOUS GAMES e11 (2014); Van Velsen et al., *supra* note 32.

[75] These criteria include functionality, validity and reliability, and data protection and privacy. Albrecht, *supra* note 74.

[76] Van Velsen et al., *supra* note 32.

[77] Brian Dolan, *Happtique Suspends Mobile Health App Certification Program*, MOBIHEALTHNEWS (Dec. 13, 2016), http://www.mobihealthnews.com/28165/happtique-suspends-mobile-health-app-certification-program [https://perma.cc/Q8VN-8XRC].

[78] Chan et al., *supra* note 74, at 1039; *see also App Evaluation Model*, AM. PSYCHIATRIC ASS'N, https://www.psychiatry.org/psychiatrists/practice/mental-health-apps/app-evaluation-model [https://perma.cc/P6WZ-U2RK] (last visited Sept. 26, 2017) (providing a rating system to rate mental health apps and emphasizing that "any decision between you and a patient is a personal decision based on many factors").

[79] *See* Eisenberg, *supra* note 30, at 347 ("[Firms] face powerful incentives to cheat in developing and selectively disclosing information about their products in order to improve sales.").

A. FDA Jurisdiction Over Digital Psychiatric Therapies

The Federal Food, Drug, and Cosmetic Act of 1938 (FDCA) gave FDA authority to oversee the safety of food, drugs, and cosmetics.[80] Congress amended the statute in 1976 to give FDA authority to require testing of high-risk devices for safety and effectiveness.[81] The statute defines a "device" broadly and inclusively.[82] A plain reading of this definition would seem to include digital psychiatric therapies (and other software treatments) either because they are "intended for use . . . in the cure, mitigation, treatment or prevention of disease" or "intended to affect the structure or any function of the body of man or other animals."[83] The definition focuses on intended use, which FDA regulations define as "objective intent of the persons legally responsible for the labeling of devices."[84] Intent is a fact-based inquiry that can be "determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article."[85] This intent is not fixed but "may change after [the article] has been introduced into interstate commerce by its manufacturer," based on the intent of a distributor or seller.[86]

For digital psychiatric therapies, intent and FDA jurisdiction will therefore depend on claims made about them in the marketplace. Claims about specific diseases and conditions will be more likely to invoke FDA oversight, whereas generalized claims about well-being or mental health will not. For example, a general "brain training" program would not be a medical device, while a more specialized claim regarding the treatment of ADHD or traumatic brain injury would be. An example from another emerging technology, direct-to-consumer genetic tests, may be instructive. On November 22, 2013, FDA sent a letter to direct-to-consumer genetic testing company 23andMe asserting that it was in violation of the FDCA.[87] FDA focused specifically

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[80] Pub. L. No. 75-717, 52 Stat. 1040 (1938), 21 U.S.C. 301 et seq.

[81] Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (1976).

[82] A "device" is defined as:

> an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—
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> (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
>
> (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
>
> (3) intended to affect the structure or any function of the body of man or other animals, and
>
> which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

21 U.S.C. § 321(h) (2012).

[83] *Id*.

[84] 21 C.F.R. § 801.4 (2016).

[85] *Id.* ("This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised.").

[86] *Id.*

[87] Letter from Alberto Gutierrez, Dir., Office of In Vitro Diagnostics & Radiological Health, Ctr. for Devices & Radiological Health, Food & Drug Admin., to Ann[e] Wojcicki, C.E.O., 23andMe, Inc. (Nov.

on the claim that the genetic test was the "first step in prevention" for diseases such as diabetes and cancer.[88] Though FDA ultimately allowed 23andMe to market its genetic test for several hereditary conditions,[89] the decision created uncertainty about the future of direct-to-consumer genetic testing.[90] Digital psychiatric therapies might similarly fall under FDA jurisdiction if developers advertise their products as having a disease-related benefit, even if their language is suggestive rather than explicit.

The line between condition-specific and general claims is not always clear, however. A company may be careful not to tout its specific product as a treatment for ADD or ADHD. The company might instead state on its website that "training cognitive skills . . . may . . . be beneficial in helping individuals with attention issues."[91] However, the suggestion of a benefit—in this case based on "anecdotal evidence" or a case study based on four siblings—could arguably place it under FDA's jurisdiction.[92] Since jurisdiction is a question of marketing claims, many digital psychiatric therapy stakeholders seem to consider the decision about whether to pursue FDA clearance a strategic choice rather than a legal requirement.[93] Legal advisors have emphasized the importance of carefully drafting marketing materials to help new software companies avoid FDA jurisdiction.[94] As a result, a large number of other

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22, 2013), http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm376296.htm [https://perma.cc/G2SW-C6C9].

[88] *Id.*

[89] *FDA Allows Marketing of First Direct-to-Consumer Tests that Provide Genetic Risk Information for Certain Conditions*, FOOD & DRUG ADMIN. (Apr. 6, 2017), https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm551185.htm [https://perma.cc/M43T-ALNS].

[90] Patricia J. Zettler et al., *23andMe, the Food and Drug Administration, and the Future of Genetic Testing*, 174 JAMA INTERNAL MED. 493, 494 (2014) ("Whether [the FDA's warning letter] marks the end of direct-to-consumer genetic testing depends on the FDA's standards for their clinical validity.").

[91] *Brain Training Software Helps Treat ADD and ADHD*, BRAINWARE SAFARI, https://mybrainware.com/brainware-safari/adhd/ [https://perma.cc/QZR8-QXZM] (last visited June 7, 2017).

[92] *Id*. ("[A]necdotally, some parents of children with ADHD and clinicians and teachers working with such individuals have noted improvements in attention and focus following use of BrainWare SAFARI."); *see also BrainWare Safari Results—A Family with ADD/ADHD*, BRAINWARE SAFARI (Mar. 10, 2008), https://brainware-wdatf4ulri9dzemoa.netdna-ssl.com/wp-content/uploads/2017/03/BWSStudy-BWSandADHDfamily-March2008.pdf [https://perma.cc/XMW7-D2Z7] (reporting anecdotal results of product's effect on family of four boys).

[93] Dan Gebremedhin & Matthew Schuster, *Overview: Health Tech Startups Innovating the Behavioral Health Space*, MOBIHEALTHNEWS (Aug. 29, 2016), http://www.mobihealthnews.com/content/overview-health-tech-startups-innovating-behavioral-health-s [https://perma.cc/T4MS-57Y6] ("A major distinction within this class of intervention is the evidence basis behind the therapy and clinical approach to the FDA. Taking the more rigorous path, a handful of companies are mirroring biochemical therapeutic commercial pathways by developing solutions rooted in clinical evidence and embarking upon randomized clinical trials with plans to submit their research to the FDA for clearance . . . .There are a large class of entrants attempting to use software as a therapeutic, but are choosing initially to bypass the rigorous clinical pathway required by the FDA. These companies are designing interventions and most often marketing them directly to consumers and/or self-insured employers."); *see also* McClurg, *supra* note 18 (reporting that four CEOs of new technologies, including digital psychiatric therapies, who "were on a panel discussing the merits and risks of choosing FDA approval . . . all agreed it depends on money, time and target market").

[94] Keith Barritt, *How To Avoid FDA Regulation of Your Medical Mobile App*, MED. DEVICE ONLINE (July 7, 2015), https://www.meddeviceonline.com/doc/how-to-avoid-fda-regulation-of-your-mobile-medical-app-0001 [https://perma.cc/A5RA-6ESM]; *see also* Robbins, *supra* note 46 ("[E]ntrepreneurs are

companies developing digital psychiatric therapies are marketing directly to consumers or employers without pursuing FDA approval or clearance (at least initially).[95]

i. Digital Psychiatric Therapies and the Practice of Medicine

Because digital psychiatric therapies (often by design) may resemble traditional therapy such as CBT, one might ask whether digital psychiatric therapies are in fact *therapy*, rather than a medical *device*.[96] The stakes of this question are high because FDA does not regulate the practice of medicine.[97] But to the extent digital psychiatric therapies rely on algorithms without human supervision, the software, not a therapist, is providing treatment. While digital psychiatric therapies are different from other medical devices, they are distinct in a way that makes them more concerning. Devices are non-metabolized articles that affect the structure or function of a person's body.[98] Medical professionals might use digital psychiatric therapies in the provision of therapy; however, digital psychiatric therapies are distinct articles and FDA retains authority to regulate such articles.[99] Because digital psychiatric therapies are an "article," rather than a process or mode of treatment, and they act directly on the function of a human's brain, they are more similar to a traditional regulated device than therapy itself.

B. FDA Classification of Digital Psychiatric Therapies

Once FDA establishes jurisdiction over a device, the Medical Device Amendments of 1976 require the agency to classify medical devices by risk.[100] Class I devices are the lowest-risk devices and are subject to general controls, such as adulteration and registration.[101] Class II devices are subject to additional special controls, which are usually device-specific.[102] These devices typically gain FDA clearance for general use after a finding of "substantial equivalence" to an existing marketed device through

finding creative ways to stay within the law, often by carefully wording their ads or by labeling their customers as research subjects.").

95 Gebremedhin & Schuster, *supra* note 93; McClurg, *supra* note 18.

96 *See* Cortez, *supra* note 17, at 450–51.

97 *See* 21 U.S.C. § 396 (2012) ("Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship."). For a history of the ways in which the federal government has left the regulation of the practice of medicine to states, see Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427, 434–53 (2015). Professor Zettler also argues that FDA's premarket review of medical devices de facto regulates the practice of medicine and that such federal regulation is beneficial when addressing national public health problems. *Id.* at 482–85.

98 21 U.S.C. § 321(h) (2012).

99 *Id.* § 396 ("This section shall not limit any existing authority of the Secretary to establish and enforce restrictions on the sale or distribution, or in the labeling, of a device that are part of a determination of substantial equivalence, established as a condition of approval, or promulgated through regulations. Further, this section shall not change any existing prohibition on the promotion of unapproved uses of legally marketed devices.").

100 Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (1976).

101 21 C.F.R. § 860.3(c)(1) (2016).

102 *Id.* § 860.3(c)(2).

what is referred to as the Premarket Notification 510(k) pathway.[103] Class III devices—those that support or sustain human life, prevent impairment of human health, or present a potentially unreasonable risk of illness or injury—are the highest-risk devices and typically require premarket approval (PMA).[104] These classifications have important implications for the amount and type of clinical data FDA will require before allowing marketing of a device. Most Class III devices require clinical data whereas Class II devices may not, and Class I devices are typically exempt from data submissions. FDA determines specific requirements for clinical studies on a case-by-case basis.

New devices, meaning devices that are not substantially equivalent to devices introduced before May 28, 1976, are presumptively Class III medical devices.[105] To determine the classification of a new medical device, companies typically refer to the *Code of Federal Regulations* (CFR), which lists cleared or approved devices and their class.[106] However, the CFR currently does not include any specific devices that would be equivalent to the devices at issue. Digital psychiatric therapies would thus presumptively be Class III medical devices.[107]

Manufacturers of low- and moderate-risk devices that are not substantially equivalent to an existing device can apply for de novo reclassification.[108] If a device receives de novo reclassification, then the device would be a Class I or Class II device and may not require a PMA application. Some digital psychiatric therapies, such as a smartphone video game intended to treat ADHD, may be good candidates for reclassification since typical use of a smartphone video game does not pose a safety risk. Depending on the specific claims developers make, FDA may reclassify some digital psychiatric therapies. However, this reclassification could raise safety and effectiveness concerns if FDA does not require developers to demonstrate clinical benefits before marketing apps.[109] Substituting an unproven device treatment for a proven pharmacological treatment, for example, could lead to adverse outcomes.

Digital psychiatric therapies that FDA does not reclassify will presumptively be Class III and likely subject to the PMA process. Traditionally, this meant the

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[103]*Premarket Notification 510(k)*, FOOD & DRUG ADMIN., http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketnotification510k/default.htm [https://perma.cc/2VHP-8YF4] (last visited Sept. 26, 2017).

[104]21 C.F.R. § 860.3(c)(1), (3) (2016).

[105]*Id.* § 860.134(a).

[106]21 C.F.R. § 860 (2016).

[107]The FDA has classified some forms of software as Class I or Class II devices; however, these classifications would not apply to digital psychiatric therapies. *E.g.*, Medical Devices; Medical Device Data Systems, 76 Fed. Reg. 8,637 (Feb. 15, 2011) (codified at 21 C.F.R. § 880.6310 (2016)) (reclassifying Medical Device Data Systems from Class III to Class I devices and exempting them from the 510(k) clearance process); Radiology Devices; Classifications for Five Medical Image Management Devices, 63 Fed. Reg. 23,385 (Apr. 29, 1998) (codified at 21 C.F.R. § 892.2050 (2016)) (classifying Picture Archiving and Communications Systems as Class II devices); Clinical Chemistry and Clinical Toxicology Devices; General Provisions and Classifications of 220 Devices, 52 Fed. Reg. 16,102, 16,113 (May 1, 1987) (codified at 21 C.F.R. § 892.2100 (2016)) (classifying Laboratory Information Systems as Class I devices).

[108]21 U.S.C. § 360c(f)(2) (2012).

[109]Although the reSET device was reviewed through the *de novo* pathway, the FDA reviewed a "multi-site, unblinded 12-week clinical trial of 399 patients who received either standard treatment or standard treatment with the addition of a desktop-based version of [reSET] which could be accessed at the clinic or at home" before permitting marketing. FOOD & DRUG ADMIN., *supra* note 11.

manufacturer must therefore provide to FDA data showing "reasonable assurance that the device is safe and effective" to market the product.[110] However, in 1997, Congress amended the FDCA to direct the Secretary to use "the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval."[111] This standard raises the question of how rigorously FDA will require tests of psychiatric mobile therapies.

Once FDA clears psychiatric mobile therapies, FDA will also have to determine how to regulate new psychiatric mobile therapies that are similar to marketed devices. Class III devices similar to those that go through the PMA process may not be eligible for the 510(k) pathway. However, if a company develops a digital psychiatric therapy similar to a marketed therapy, the company may argue it should be able to use the 510(k) process to gain approval without independently demonstrating safety and effectiveness. For other types of devices, the 510(k) process has allowed manufacturers to expedite the marketing of similar devices; 510(k) applications are deemed to be substantially equivalent about 80 percent of the time.[112]

C. FDA Guidance Pertaining to Digital Psychiatric Therapies

FDA often uses guidance rather than rulemaking to implement its preferred policies, including with regard to software, relying on the regulatory flexibility that guidance allows.[113] FDA first attempted to address questions about its oversight of digital devices through a document entitled "FDA Policy for the Regulation of Computer Products 11/13/89 (Draft)." FDA withdrew that document in 2005 without finalizing it,[114] and FDA later argued "it would be impractical to adopt one 'software' or 'computer' policy to address all computer and software medical devices."[115]

In areas at the forefront of technological development, including those relevant to digital psychiatric therapies, FDA has continued to regulate through policy guidance. In the past few years, FDA has released guidance documents related to its position on mobile apps[116] and low-risk general wellness products,[117] as well as a draft policy on

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[110]21 C.F.R. § 860.7(c)(1) (2016); *see generally id.* § 860.7.

[111]Food and Drug Administration Modernization Act of 1997, Pub. L. No. 101-115, title II, § 205, 111 Stat. 2353, 2373 (1997) (codified at 21 U.S.C. § 360c(a)(3)(D)(ii)).

[112]*See* Zachary Brennan, *FDA Sees Record-High PMA Approval Rate for 2015*, REG. AFF. PROF. SOC'Y (Nov. 11, 2015), http://www.raps.org/Regulatory-Focus/News/2015/11/11/23580/FDA-Sees-Record-High-PMA-Approval-Rate-for-2015/ [https://perma.cc/6GDE-CRVE] (showing 510(k) applications are determined to be substantially equivalent approximately 80% of the time).

[113]Cortez, *supra* note 4, at 1218–23. For a history and discussion of the FDA's use of guidance generally, see K.M. Lewis, *Informal Guidance and the FDA*, 66 FOOD & DRUG L.J. 507 (2011); *see also* CARPENTER, *supra* note **Error! Bookmark not defined.**, at 357–60.

[114]Annual Comprehensive List of Guidance Documents at the Food and Drug Administration, 70 Fed. Reg. 824, 892 (Jan. 5, 2005).

[115]Medical Devices; Medical Device Data Systems, *supra* note 107, at 8638.

[116]MMA GUIDANCE, *supra* note 1.

[117]FOOD & DRUG ADMIN., GENERAL WELLNESS: POLICY FOR LOW-RISK DEVICES—GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF (2016) [hereinafter GENERAL WELLNESS GUIDANCE], http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm429674.pdf [https://perma.cc/7RTT-CTDU].

updates to software, including software connected to a hardware medical device and standalone software.[118]

i. Guidance for Mobile Medical Applications

FDA's most recent guidance aimed at regulating software, released in 2013 and updated in 2015, uses the term "mobile medical applications."[119] This framework is intended to be inclusive of software used both by consumers and medical practitioners, while recognizing that not all mobile applications are medical devices. The guidance states that a "mobile medical app" (MMA) is "a mobile app that meets the definition of device in section 201(h) of the [FDCA]; it either is intended: to be used as an accessory to a regulated medical device; or to transform a mobile platform into a regulated medical device."[120]

The document clarifies that "[i]n general, if a mobile app is intended for use in performing a medical device function (i.e., for diagnosis of disease or other conditions, or the cure, mitigation, treatment, or prevention of disease) it is a medical device, regardless of the platform on which it is run."[121] Mobile apps that are medical devices will still be classified and subject to the appropriate controls.[122]

The document also lays out the agency's plans for regulating MMAs. The stated principle undergirding the framework is safety: "FDA intends to apply its regulatory oversight to only those mobile apps that are medical devices and whose functionality could pose a risk to a patient's safety if the mobile app were to not function as intended."[123] Accordingly, the document divides the world of MMAs into two categories: (1) mobile apps that are the focus of FDA's regulatory oversight and (2) mobile apps for which FDA intends to exercise enforcement discretion (i.e., FDA does not intend to enforce requirements under the FDCA).[124]

It is unclear, however, how digital psychiatric therapies fit into this framework, which does not directly consider the possibility of this type of application. Most, if not all, of these therapies meet the statutory definition of "device." Therefore, the question is whether FDA will exercise enforcement discretion. The guidance categorizes which medical apps are subject to enforcement:

> 1. Mobile apps that are *an extension of one or more medical devices* by connecting to such device(s) for purposes of controlling the device(s) or for use in active patient monitoring or analyzing medical device data.
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> . . . .

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[118]FOOD & DRUG. ADMIN., DECIDING WHEN TO SUBMIT A 510(K) FOR A SOFTWARE CHANGE TO AN EXISTING DEVICE: DRAFT GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF (2016) [hereinafter DRAFT 510(K) GUIDANCE], http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm514737.pdf [https://perma.cc/2SQL-J9Y8].

[119]MMA GUIDANCE, *supra* note 1. It is worth noting that FDA is in the process of assessing how to revise this document in light of recent developments such as the 21st Century Cures Act, discussed *infra*.

[120]*Id.* at 7 (footnote omitted).

[121]*Id.* at 8.

[122]*Id.* at 13.

[123]*Id.*

[124]*Id.* at 13–18.

> 2. Mobile apps that *transform the mobile platform into a regulated medical device* by using attachments, display screens, or sensors or by including functionalities *similar to those of currently regulated medical devices*. Mobile apps that use attachments, display screens, sensors or other such similar components to transform a mobile platform into a regulated medical device are required to comply with the device classification associated with the transformed platform.
>
> . . . .
>
> 3. Mobile apps that become a regulated medical device (software) by performing patient-specific analysis and providing patient-specific diagnosis, or treatment recommendations. *These types of mobile medical apps are similar to or perform the same function as those types of software devices that have been previously cleared or approved.*[125]

The italicized phrases highlight the link between mobile apps subject to enforcement and other regulated devices. Although the stated principle underlying enforcement is the level of risk to safety, this categorization suggests FDA primarily intends to enforce the FDCA for MMAs that connect to a currently regulated device or perform similar functions. This reading creates an issue for digital psychiatric therapies. Arguably, software-based therapies fall under the second category since they may transform a mobile platform into a medical device. However, it is unclear whether the platform operating the app becomes a "regulated device." Furthermore, all the examples given in the guidance are for patient monitoring, such as "attachment of a blood glucose strip reader to a mobile platform to function as a glucose meter" and "a mobile app that uses the built-in accelerometer on a mobile platform to collect motion information for monitoring sleep apnea."[126]

Presumably, many developers will want to avoid the FDCA's requirements and accordingly may believe their products do not fall under any of the above categories that subject the devices to enforcement. Although the product is a device because it is intended to serve a treatment function, the developer may conclude that it is one where FDA exercises enforcement functions. A reasonable analysis could conclude that a smartphone video game intended to treat ADHD is not an extension of a medical device because it does not connect to a medical device. Nor would the app necessarily transform the mobile platform into a regulated medical device such as an ultrasound because the app would not require external attachments, display screens, or sensors. Finally, the smartphone video game would not perform the same function as a previously cleared or approved software device. These MMAs instead tend to serve as a substitute for, or complement to, clinicians who would otherwise provide this care.

At the same time, the guidance does not clearly exclude digital psychiatric therapies and other software-based medical treatments from enforcement. The list of devices for which FDA does not plan to enforce focuses on MMAs that help users self-manage conditions or provide information.[127] This formulation suggests that crossing into the arena of treatment may trigger FDA enforcement.

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[125] *Id.* at 14–15 (emphasis added) (footnotes omitted).

[126] *Id.* at 14.

[127] FDA plans not to enforce the requirements of the FDCA for mobile apps that:

However, the line between information or self-management and treatment is not always an obvious one for psychiatric diseases. A product that focuses on physical illness might use interactive coaches, tracking, and data analysis to build healthy habits and prevent heart disease or diabetes.[128] Even if the product makes a claim about prevention of a specific disease, the guidance suggests FDA will not enforce the FDCA against this type of medical device if these functions do not treat the disease or provide specific recommendations. The treatment of a behavioral health disorder, however, might use similar modalities. Pear Therapeutics' reSET app treats substance use disorder with "a series of self-guided cognitive behavioral modules" (i.e., educational modules followed by a quiz on the covered material).[129] It is easy to equate these products' modalities;[130] however, the key distinguishing factor is whether the app provides treatment. Although there are "health coach" apps for mental illness that provide general information or refer patients to help in emergencies,[131] against which FDA presumably will not enforce the FDCA, the guidance does not specify how FDA will regulate software that does provide treatment.

The guidance therefore creates some confusion for digital psychiatric therapies. On the one hand, digital psychiatric therapies do not fit neatly into the categories in the MMA guidance. Their possible exclusion suggests the requirements of the FDCA do not apply to them. On the other hand, assuming developers make disease-specific treatment claims, they do not simply provide information but rather treat conditions. The focus on treatment suggests they should be subject to enforcement. FDA has continued to provide information in this area, including additional examples of regulated and unregulated functions, as well as a service that allows companies to

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• Help patients (i.e., users) self-manage their disease or conditions without providing specific treatment or treatment suggestions;

• Provide patients with simple tools to organize and track their health information;

• Provide easy access to information related to patients' health conditions or treatments;

• Help patients document, show, or communicate potential medical conditions to health care providers;

• Automate simple tasks for health care providers;

• Enable patients or providers to interact with Personal Health Record (PHR) or Electronic Health Record (EHR) systems; or

• Intended to transfer, store, convert format, and display medical device data in its original format from a medical device.

Id. at 15–16.

[128]*Our Solution*, OMADA HEALTH, https://www.omadahealth.com/solution [https://perma.cc/P995-VPVV] (last visited Sept. 26, 2017); *Take a Sneak Peek*, OMADA HEALTH, https://www.omadahealth.com/take-a-sneak-peek [https://perma.cc/WHD8-UJJH] (last visited Sept. 26, 2017).

[129]Gerald Cochran et al., *Web-based Treatment for Substance Use Disorders: Differential Effects by Primary Substance*, 45 ADDICTIVE BEHAVS. 191, 191 (2015); *reSET*, PEAR THERAPEUTICS, https://peartherapeutics.com/reset/ **[**https://perma.cc/688T-BUC3**]** (last visited Sept. 26, 2017).

[130]*See* Joe Riley, *Software as a Drug*, HEALTH CARE BLOG (Nov. 18, 2016), http://thehealthcareblog.com/blog/2016/11/18/software-as-a-drug/ [https://perma.cc/S9LR-WC7L] (comparing products that track indicators of chronic illness such as Omada Health's to those that treat behavioral health disorders such as Pear Therapeutics' reSET).

[131]*E.g.*, CODE BLUE, http://codeblue.io [https://perma.cc/HHR8-WGY2] (last visited Sept. 26, 2017); U.S. Dep't of Veterans Affairs, *Mobile App: PTSD Coach*, VA.GOV, http://www.ptsd.va.gov/public/materials/apps/PTSDCoach.asp [https://perma.cc/3FRG-HLRT] (last visited Sept. 26, 2017).

contact FDA to ask questions related to MMAs.[132] However, since the guidance does not seem to contemplate enforcing the FDCA's requirements for MMAs that treat disease, it seems FDA did not contemplate MMAs intended to treat disease or chose not to regulate these MMAs.[133] Although FDA can and may still choose to pursue enforcement actions, the document seems to indicate some reluctance on the part of FDA to prioritize enforcing the FDCA against software treatments.

ii. Guidance for Low-Risk General Wellness Devices

FDA has also released final guidance clarifying the policy on low-risk products intended to promote a healthy lifestyle.[134] For this set of products, FDA does not intend to determine whether they are indeed devices nor enforce compliance with the FDCA and its implementing regulations.[135] To qualify, a product must be "intended for only general wellness use" and "present a low risk to the safety of users and other persons."[136] The guidance explicitly applies to both mobile applications and physical products.[137]

The guidance subdivides general wellness use into two categories. The first category does not reference a specific disease or condition but instead makes claims related to general health, such as weight management or mental acuity.[138] The second category consists of devices intended to promote, track and/or encourage choices that help reduce the risk of certain chronic diseases or help patients to live better with these conditions.[139] Claims in the second category (that lifestyle choices may affect health outcomes) "should be generally accepted," meaning "such associations are described in peer-reviewed scientific publications or official statements made by healthcare professional organizations."[140] As under the FDCA itself, FDA enforcement for many devices will turn on the nature of the marketed claims. Therefore, the most innovative condition-specific therapies likely will not avoid FDCA enforcement under this policy.

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[132]*Mobile Medical Applications*, FOOD & DRUG ADMIN, https://www.fda.gov/MedicalDevices/DigitalHealth/MobileMedicalApplications/default.htm [https://perma.cc/7SWF-URB2] (last visited Nov. 28, 2017).

[133]Any oversight likely does not reflect intentional bias by FDA. It is important, however, to situate this assumption in society's historical failure to provide adequate care for the mentally ill. *See, e.g*, Heidi Ledford, *Medical Research: If Depression Were Cancer*, 515 NATURE 182 (2014); *A Neglect of Mental Illness*, SCI. AM., Mar. 2012, at 8; Liz Szabo, *Cost of Not Caring: Nowhere To Go*, USA TODAY (May 12, 2014), http://www.usatoday.com/story/news/nation/2014/05/12/mental-health-system-crisis/7746535/ [https://perma.cc/BBM3-RGNQ].

[134]GENERAL WELLNESS GUIDANCE, *supra* note 117.

[135]*Id.* at 2.

[136]*Id.* (emphasis in original). The document defines low-risk products as products that are not invasive, not implanted, and do not "involve an intervention or technology that may pose a risk to the safety of users and other persons if specific regulatory controls are not applied." *Id.* at 5.

[137]*Id.* at 6–7.

[138]*Id.* at 3.

[139]*Id.* at 4.

[140]*Id.*

iii. Draft Guidance for 510(k) Submissions After a Software Change to an Existing Device

FDA has also released a draft document for public comment detailing when FDA will expect changes to software (such as updates or more extensive modifications) to result in filing of a new 510(k) application.[141] FDA regulations require a device manufacturer to submit a new 510(k) when a modification "could significantly affect the safety or effectiveness of the device" or represents a "major change or modification" in the device's intended use.[142] The draft document exempts certain software changes from triggering a 510(k)—such as improvements in cybersecurity—while specifying others that are likely to require a 510(k)—such as changes that would affect the device's "clinical functionality or performance specifications that are directly associated with the intended use of the device."[143]

Although FDA has not yet finalized this guidance, the draft raises concerns about the 510(k) process. For most health-related software, the 510(k) process is likely adequate since manufacturers that make changes that might affect the safety or performance of the software must report those changes to FDA.[144] For digital psychiatric therapies, however, the 510(k) process seems like a poor fit. Determining substantial equivalence for software treatments can be difficult without understanding how users will interact with it. Moreover, the 510(k) process, over time, allows for significant drift from the original device (which itself may or may not be adequately tested).[145] When a developer's claims warrant additional clinical data, an adequate clearance process should include the submission of data that demonstrate the "substantially equivalent" device is safe and effective.

Once a digital psychiatric therapy is on the market, developers' ability to expand the device's marketing through the 510(k) process may curb the incentive to conduct rigorous studies for new indications. A 510(k) submission can rely on analogies to previous studies,[146] so if the device's new intended use is similar to the marketed use and eligible for the 510(k) process,[147] companies will likely attempt to avoid conducting additional studies for new indications. If FDA does not require additional studies, companies may not generate adequate information about the safety and effectiveness of the software for a new indication. For example, Akili's Project: EVO platform "is currently being tested in a variety of clinical studies in multiple patient populations around the globe, including ADHD, autism, depression, and traumatic

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[141]DRAFT 510(K) GUIDANCE, *supra* note 118.

[142]21 C.F.R. § 807.81(a)(3) (2016).

[143]DRAFT 510(K) GUIDANCE, *supra* note 118, at 11.

[144]It is worth noting, however, that from 2011–15 the FDA issued recalls of 627 medical devices for software-related reasons, including 12 high-risk recalls. Of these high-risk recalls, 11 of the devices reached the market through 510(k) review and one was exempt from FDA regulatory review because the FDA deemed review unnecessary. Jay G. Ronquillo & Diana M. Zuckerman, *Software-Related Recalls of Health Information Technology and Other Medical Devices: Implications for FDA Regulation of Digital Health*, 95 MILBANK Q. 535, 541–43 (2017).

[145]Brent M. Ardaugh et al., *The 510(k) Ancestry of a Metal-on-Metal Hip Implant*, 368 NEW ENG. J. MED. 967 (2013).

[146]*See* 21 C.F.R. § 807.92(b) (2016).

[147]*See* 21 C.F.R. § 807.92(a)(5) (2016).

brain injury."[148] Since this set of conditions is diverse, the therapy will likely have different effects on each. A less scrupulous company could attempt to use the 510(k) process to extend the software's marketed indications without studying its effects if FDA does not consistently require clinical data for clearance.

D. FDA Precertification Pilot Program

In July 2017, FDA announced a pilot program intended to streamline the review process for medical software. The Digital Health Software Precertification Program, also known as "PreCert," will expedite regulatory review for companies with "an existing track record" in software and that demonstrate "a culture of quality and organizational excellence."[149] Precertified companies could receive exemptions from FDA regulatory review or receive faster premarket review that includes the submission of less data.[150] In order to participate, companies must provide FDA access to information about the firm's quality management, collect postmarket data and provide it to FDA, and provide access for site visits.[151] In January 2018, FDA will hold a public workshop to review the program.[152] Soon after introducing the program, FDA Commissioner Scott Gottlieb announced the nine companies initially selected to participate in the program.[153]

Details about the program at this time are somewhat sparse, but developers of digital psychiatric therapies and other software treatments such as Pear Therapeutics are taking advantage of the program. Early analysis of the program suggests that it may not assure safety and effectiveness[154] because the program's structure rests on the dubious assumption that company performance is a meaningful proxy for device performance.[155]

E. Fragmentation of the Regulatory Framework

A number of government actors other than FDA influence the legal and regulatory landscape for MMAs, leading to a fragmented approach. In general, Congress and

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[148]AKILI, *supra* note 20.

[149]Scott Gottlieb, *FDA Announces New Steps to Empower Consumers and Advance Digital Healthcare*, FOOD & DRUG ADMIN. (July 27, 2017), https://blogs.fda.gov/fdavoice/index.php/2017/07/fda-announces-new-steps-to-empower-consumers-and-advance-digital-healthcare/ [https://perma.cc/523G-WG9J]; *see also Digital Health Software Precertification (PreCert) Program*, FOOD & DRUG ADMIN., https://www.fda.gov/MedicalDevices/DigitalHealth/UCM567265 [https://perma.cc/6BHP-Z4TE] (last visited Sept. 26, 2017).

[150]*Id.*

[151]*Id.*

[152]*Id.*

[153]Press Release, Food & Drug Admin., FDA Selects Participants for New Digital Health Software Precertification Pilot Program (Sept. 26, 2017), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm577480.htm [https://perma.cc/4XDG-6SYN] (announcing the selection of Apple, Fitbit, Johnson & Johnson, Pear Therapeutics, Phosphorus, Roche, Samsung, Tidepool, and Verily).

[154]Nathan G. Cortez et al., *Questions About The FDA's New Framework For Digital Health*, HEALTH AFF. BLOG (Aug. 16, 2017), http://healthaffairs.org/blog/2017/08/16/questions-about-the-fdas-new-framework-for-digital-health [https://perma.cc/ZAJ6-LATP].

[155]Theodore T. Lee & Aaron S. Kesselheim, The FDA's PreCert Pilot Program for Digital Health Software: Weighing the Benefits and Risks (unpublished manuscript) (on file with author).

federal agencies have permitted and facilitated the development of mobile health.[156] Congress has recently pulled back FDA's jurisdiction over digital health by removing certain software functions from the definition of a "device."[157] However, some agencies have demonstrated an appetite for regulating digital psychiatric therapies and other software-based medical devices. For example, Federal Trade Commission (FTC) has initiated successful enforcement actions against fraudulent claims.

i. Congress

Congress has not directly addressed the question of digital psychiatric therapies; however, it has been quite active in digital health more generally.[158] Members of Congress have introduced several bills proposing to amend FDA's substantive statute to remove certain MMAs and health technologies from FDA's jurisdiction.[159] Some elected officials have expressed a desire to override FDA regulatory framework because it is "bad news for health IT innovation."[160]

These efforts recently culminated in the 21st Century Cures Act, which amended the FDCA to limit FDA's jurisdiction over certain types of software.[161] In particular, it removed from the definition of "device" (and therefore FDA's jurisdiction) certain software functions, including those intended to maintain or encourage a healthy lifestyle (if "unrelated to the diagnosis, cure, mitigation, prevention or treatment of a disease or condition"), or to serve as electronic patient records.[162] If a device has multiple functions, then only the functions specifically exempted by the amended law are unregulated by FDA.[163] The law also provides that FDA can reassert jurisdiction over a software function through a final order (after notice and comment) that finds use of the software function would be "reasonably likely to have adverse health consequences."[164]

Many digital psychiatric therapies arguably have the exempted software functions since they may provide general lifestyle recommendations and/or store patient data. However, to the extent the devices cross into treatment, FDA would still have jurisdiction over digital psychiatric therapies as a device. Moreover, given FDA's

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[156]With the possible exception of the Federal Trade Commission (FTC), federal agencies have played a role that facilitates the development and dissemination of mobile health technologies without regard to efficacy. For a broader discussion of the role of FTC and the Federal Communications Commission (FCC) in mobile health generally, see Cortez, *supra* note 4, at 1200, 1211–17.

[157]Pub. L. No. 114-255 (2016), § 3060, 130 Stat. 1033, 1130 (to be codified at 21 U.S.C. § 360j(o)).

[158]Although for many years Congress showed little interest in FDA regulation of software, significant federal investment in health information technology and the rise of mobile devices has recently elicited its attention. Cortez, *supra* note 17, at 442–43.

[159]*E.g.*, Sensible Oversight for Technology which Advances Regulatory Efficiency Act, H.R. 2396, 114th Cong. (2015); Medical Electronic Data Technology Enhancement for Consumers' Health Act, S. 2977, 113th Cong. (2014); Preventing Regulatory Overreach to Enhance Care Technology Act of 2014, S. 2007, 113th Cong. (2014); Sensible Oversight for Technology which Advances Regulatory Efficiency Act of 2013, H.R. 3303, 113th Cong. (2013).

[160]Fischer and King, *supra* note 29.

[161]Pub. L. No. 114-255 (2016), § 3060, 130 Stat. 1033, 1130 (to be codified at 21 U.S.C. § 360j(o)).

[162]*Id.*

[163]*Id.*

[164]*Id.*

reluctance to regulate general wellness devices,[165] the 21st Century Cures Act likely does not represent a significant change for most digital psychiatric therapies.[166]

The 21st Century Cures Act also includes provisions that will likely "reduce the amount and rigor of clinical testing required before new drugs and devices can be approved for use."[167] The implementation of the Act may therefore lower FDA's standards for safety and effectiveness, which would allow medical devices generally, and digital psychiatric therapies specifically, to navigate FDA process with less rigorous testing than is currently required.

ii. FTC

FTC has pursued enforcement actions against mobile health companies that made claims without adequate scientific evidence, resulting in bans on future claims and monetary penalties. FTC's mandate is to protect consumers from fraud and deception, which it accomplishes through a variety of means including legal enforcement and consumer and business education. In the mobile health arena, it has initiated enforcement actions against a variety of software products, including a game that the developer claimed could reverse age-related vision degeneration and an app that the developers claimed could detect melanoma by analyzing photos of skin lesions.[168]

The FTC enforcement suit most relevant to digital psychiatric therapies addressed the brain game industry. In January 2016, FTC filed a complaint against Lumosity based on representations that the Lumosity "brain training" program will "protect against . . . age-related conditions such as mild cognitive impairment, dementia, and Alzheimer's disease; and will reduce cognitive impairment associated with . . . post-traumatic stress disorder, traumatic brain injury, attention deficit hyperactivity disorder, Turner syndrome, stroke, and other health conditions."[169] The case settled for $2 million and a permanent injunction on future deceptive conduct.[170] Notably, the

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[165]FOOD AND DRUG ADMIN., *supra* note 117.

[166]Some commentators have raised the issue that future amendments to the FDCA may threaten FDA's ability to regulate health-related software. These commentators draw analogies to Congressional action precluding FDA regulation of dietary supplements. *See, e.g.*, Cortez, *supra* note 17, at 453; Natalie R. Bilbrough, Note, *The FDA, Congress, and Mobile Health Apps: Lessons from DSHEA and the Regulation of Dietary Supplements*, 74 MD. L. REV. 921, 949–54 (2015) (arguing that the FDA's tenuous jurisdiction with regard to MMAs is analogous to its regulation over dietary supplements prior to Congress reclassifying dietary supplements as food).

[167]Aaron S. Kesselheim & Jerry Avorn, *New "21st Century Cures" Legislation: Speed and Ease vs Science*, 317 J. AM. MED. ASS'N. 581, 581 (2017).

[168]*E.g.*, Complaint, In re Carrot Neurotechnology, Inc., No. C-4567 (F.T.C. Feb. 23, 2016), https://www.ftc.gov/enforcement/cases-proceedings/142-3132/carrot-neurotechnology-inc-matter-ultimeyes [https://perma.cc/4URL-X3DT]; Complaint, In re Health Discovery Corp., No. C-4516 (F.T.C. Apr. 13, 2015), https://www.ftc.gov/enforcement/cases-proceedings/132-3211/health-discovery-corporation-melapp-matter [https://perma.cc/W8ST-WHS4]; Complaint, F.T.C. v. New Consumer Solutions LLC et al., No. 15-C-1614 (N.D. Ill. Feb. 23, 2015), https://www.ftc.gov/enforcement/cases-proceedings/132-3210/new-consumer-solutions-llc-mole-detective [https://perma.cc/3PYE-L7MG].

[169]Complaint at 5, F.T.C. v. Lumos Labs, Inc. d/b/a Lumosity, No. 3:16-cv-00001 (N.D. Cal. Jan. 4, 2016), ECF No. 1, https://www.ftc.gov/system/files/documents/cases/160105lumoslabscmpt.pdf [https://perma.cc/5ME3-A3Y9].

[170]Stipulated Final Judgment and Order for Permanent Injunction and Other Equitable Relief at 5-9, F.T.C. v. Lumos Labs, Inc. d/b/a Lumosity, No. 3:16-cv-00001 (N.D. Cal. Jan. 8, 2016), ECF No. 10, https://www.ftc.gov/system/files/documents/cases/160105lumoslabsstip.pdf [https://perma.cc/7JZL-GK7Y]. These qualifications to the settlement are not atypical of FTC enforcement actions in digital health. *See, e.g.*, Stipulated Final Judgment and Order for Permanent Injunction and Other Equitable Relief against

settlement did not prohibit marketing consistent with FDA-approved labeling.[171] The settlement also allowed the possibility of labeling Lumosity products as a drug in the future.[172] It is unlikely FDA or software developers would pursue a new drug application or another form of drug labeling since the existing regulatory structure considers software to be a medical device. There is recognition, however, that digital psychiatric therapies have the potential to function in a way that treats patients' underlying conditions.

FTC enforcement has its limits as a strategy for regulating digital psychiatric therapies. Because agency resources are limited and FTC must accordingly decide which enforcement actions to prioritize, FTC will not be able to pursue all claims that lack scientific evidence.[173] FTC is also often more lenient than FDA in its interpretation of what constitutes a fraudulent therapeutic claim.[174] This discrepancy between FDA and FTC's interpretations reflect their different missions: FDA promotes public health while FTC protects consumers from unfair trade practices. Perhaps in an attempt to overcome some of these limitations, FTC has launched an online questionnaire in collaboration with other federal agencies (including FDA) that is intended to help mobile health app developers identify which federal laws apply and how.[175] Although this tool has the potential to improve compliance with the law, it does not address the underlying problem of safety and effectiveness of MMAs. FTC is therefore likely to play (at most) a role that is supplementary to FDA regulation.

iii. States

Although device regulation is historically an area of federal regulation, states are also beginning to show interest in regulating digital health. For example, New York recently settled claims against three MMA developers, two of which claimed their products could accurately measure heart rate while the third claimed its app transformed a smartphone into a fetal heart monitor.[176] The state had alleged the

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Defendants Kristi Zuhlke Kimball and New Consumer Solutions LLC at 8-9, No. 1:15-cv-01614 (N.D. Ill. Apr. 30, 2015), ECF No. 27, https://www.ftc.gov/system/files/documents/cases/new_consumer_solutions_5-1-15.pdf [https://perma.cc/UJQ8-V3LV].

[171]Stipulated Final Judgment and Order for Permanent Injunction and Other Equitable Relief, *supra* note 170, at 8.

[172]*Id.* at 8.

[173]Decisions about enforcement discretion are complex. For a leading discussion of judicial understandings of enforcement discretion, see Heckler v. Chaney, 470 U.S. 821, 831–32 (1985) ("This Court has recognized on several occasions over many years that an agency's decision not to prosecute or enforce, whether through civil or criminal process, is a decision generally committed to an agency's absolute discretion. This recognition of the existence of discretion is attributable in no small part to the general unsuitability for judicial review of agency decisions to refuse enforcement . . . .[A]n agency generally cannot act against each technical violation of the statute it is charged with enforcing. The agency is far better equipped than the courts to deal with the many variables involved in the proper ordering of its priorities.") (citations omitted).

[174]*See* PETER BARTON HUTT, RICHARD A. MERRILL & LEWIS A. GROSSMAN, FOOD AND DRUG LAW: CASES AND MATERIALS 456–58 (4th ed. 2014).

[175]*Mobile Health Apps Interactive Tool*, FED. TRADE COMMISSION (Apr. 2016), https://www.ftc.gov/tips-advice/business-center/guidance/mobile-health-apps-interactive-tool. [https://perma.cc/KZV3-84UC].

[176]Press Release, N.Y. State Office of Attorney Gen., A.G. Schneiderman Announces Settlements with Three Mobile Health Application Developers for Misleading Marketing and Privacy Practices (Mar.

companies were marketing their apps without valid scientific evidence to support their claims and had inadequate privacy protections.[177] Other state attorneys general who are dissatisfied with the level of consumer protection the federal government is providing in this area may pursue similar claims.[178] Although the apps involved in the New York settlements were monitoring tools rather than treatments, a state could conceivably pursue claims against digital psychiatric therapy developers. As long as FDA's framework for digital psychiatric therapies and other MMAs remains unclear, these state efforts may overlap with or be preempted by federal regulation and lead to additional confusion.

III. CONCERNS RAISED BY DIGITAL PSYCHIATRIC THERAPIES AND OTHER SOFTWARE TREATMENTS

FDA's current regulatory framework is inadequate when applied to digital psychiatric therapies and other software treatments because the framework does not specifically address these devices and may not ensure their safety and effectiveness. In particular, FDA guidance does not clearly state whether FDA will enforce the requirements of the FDCA for these products and fails to specify how the 510(k) process will apply. In addition, despite safety and effectiveness concerns associated with digital psychiatric therapies, there is little incentive for developers to conduct rigorous clinical studies under the status quo unless FDA requires it for a specific product. However, raising FDA clearance or approval standards may hurt innovation because (as is often argued of government regulation) the regulatory burden disproportionately affects smaller companies. Although this paper has focused on digital psychiatric therapies in order to provide concrete examples, these concerns can also apply to software treatments more broadly.

A. Existing Regulation Does Not Directly Consider Software Treatments

The formulation of the existing regulatory approach makes it unclear whether and how the scheme will apply to software treatments. FDCA enforcement and the 510(k) process are areas of particular uncertainty.

As discussed above, existing FDA guidance does not clarify when the FDCA will be enforced. Many stakeholders claim this type of regulatory uncertainty makes it more difficult for developers to bring new technologies to market because the unknown cost and delay of moving through regulatory processes may deter developers.[179] Some software treatments may be able to avoid the FDCA's jurisdiction by not demonstrating an intent to treat or mitigate the symptoms of a specific disease or condition. However, other software treatments will fall under the jurisdiction of the

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23, 2017), https://ag.ny.gov/press-release/ag-schneiderman-announces-settlements-three-mobile-health-application-developers [https://perma.cc/SZ2A-V244].

[177] *Id.*

[178] Stephanie Baum, *How Should Digital Health Vendors Interpret New York's Move To Flex Its Regulatory Muscle?*, MEDCITY NEWS (May 24, 2017, 5:27PM), http://medcitynews.com/2017/05/will-states-flex-regulatory-muscle-with-digital-health-vendors/ [https://perma.cc/ZXD8-XZMY].

[179] Letter from Access Integrity, *supra* note 19; s*ee also* Letter from Thompson on behalf of mHealth Regulatory Coalition, *supra* note 31.

FDCA, and FDA should clearly state whether it plans to enforce the FDCA's requirements for those devices.

One regulatory approach might be to let FTC handle manufacturer claims that venture beyond clinically proven studies. As discussed above, FTC has successfully pursued enforcement actions against multiple software developers that made health claims without adequate scientific evidence.[180] However, in the area of digital psychiatric therapies and other software treatments, FTC currently defers to FDA-based standards and does not enforce them to the same extent FDA would or could. The FTC settlement against Lumosity did not prohibit marketing consistent with FDA-approved labeling.[181] Moreover, giving primary enforcement responsibility to FTC would not keep unsafe and ineffective software treatments off the market. FTC does not formally enforce the FDCA and can only address fraudulent claims after software treatments are already available to consumers. Although this approach might result in more marketed products, FTC enforcement alone would run the risk of subjecting customers to unsafe and/or ineffective products.[182]

In addition, the degree to which the general 510(k) process would apply is unclear. Would a digital psychiatric therapy or other software treatment be able to piggyback on a previously approved or cleared device? It may not be a wise regulatory decision to freely allow software treatments access to the 510(k) pathway without requiring clinical data given the potential difficulty of determining whether two pieces of software are substantially equivalent. Another issue for the 510(k) process is that technology today frequently relies on platforms, a group of technologies used as a base for other applications, process, or technologies. Platforms make it less clear when applications are distinct. Platforms also pose the question of whether companies can market the same therapy for multiple conditions or indications without demonstrating safety and effectiveness through the PMA process. Some manufacturers have already expressed interest in using the same platform to treat multiple conditions.[183] The 510(k) process may not be appropriate for software treatments without clinical data that demonstrates products are safe and effective for all marketed indications. Although FDA makes case-by-case determinations and can require clinical data for specific software treatments, the 510(k) process, unlike the PMA process, does not require clinical studies by default.

B. Digital Psychiatric Therapies and Other Software Treatments May Be Unsafe

Given the prevalence of computer screens and the frequency with which today's consumer interacts with digital devices, some people may argue that most apps do not pose a direct safety threat. FDA's typical prioritization for devices, which is to focus on devices that present the highest risk to patients, therefore may not always be appropriate for the realities of today's medical technology. However, the safety

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[180] *See supra* note 167 and accompanying text.

[181] Stipulated Final Judgment and Order for Permanent Injunction and Other Equitable Relief, *supra* note 170.

[182] *See infra* Parts IV. B and IV. C.

[183] AKILI, *supra* note 20 ("The Project: EVO™ platform is currently being tested in a variety of clinical studies in multiple patient populations around the globe, including ADHD, autism, depression, and traumatic brain injury.").

framework does apply to digital psychiatric therapies and other software treatments. MMAs may contribute to specific risks (such as poor lifestyle or clinical decisions), may have inherent risks themselves (such as risky intended functions or inaccurate content), and may have additional contextual risks (such as inappropriate usage or errors going undetected).[184] FDA's record with software suggests that software can contribute to medical device risk. A study of medical software found that from 2011 to 2015, 627 medical devices were subject to recall because of software defects.[185] These defects include malfunctions that could lead to premature ventilator stoppage or the storage of data that corresponded to the incorrect patient.[186] Of these recalls, 12 were high-risk and 592 were moderate-risk.[187] Eleven of the devices subject to high-risk recalls went through the 510(k) pathway and the last was exempt from regulatory review.[188] The authors of the study could not confirm that FDA considered clinical evidence for any of the devices.[189] In general, software treatments lack clinical study, which further contributes to uncertainty about safety.[190] Specific software treatments may have unintended consequences that put patients' health at risk, such as a smartphone app intended to reduce alcohol intake that may instead increase drinking.[191] As a result, these treatments might actually worsen conditions they are intended to treat.

In addition, untreated or poorly treated conditions can lead to adverse outcomes for the patient or others. The lack of conformity with established CBT principles for most CBT-based apps suggests that patients may not be getting adequate treatment.[192] Other apps might provide poor or incorrect guidance. One app for patients with BD recommended drinking a shot of hard alcohol as a sleep aid when experiencing a manic episode, and another suggested that BD is contagious because it "can transfer to another relative if they spend too much time with you and listen to your depressive life."[193] Providing incorrect information may lead to patients engaging in unsafe behaviors (in this case, drinking when manic or self-isolation). This safety problem is most apparent when digital psychiatric therapies or other software treatments serve as a substitute for other, more effective, treatments. For example, if a patient were to use an app or virtual-reality product that does not effectively treat PTSD in lieu of a drug that does, the patient's psychiatric illness might lead to an adverse outcome (e.g., substance abuse or suicide). One product in development claims to treat PTSD through

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[184]Thomas Lorchan Lewis & Jeremy C. Wyatt, *Health and Mobile Medical Apps: A Framework to Assess Risk*

and Promote Safer Use, 16 J. MED. INTERNET RES. e210, 3 (2014).

[185]Ronquillo & Zuckerman, *supra* note 144, at 536.

[186]*Id.* at 543–44.

[187]*Id.* at 541.

[188]*Id.* at 541–43.

[189]*Id.* at 542 (finding that nonclinical studies were available for 10 of the devices and information about the evidence before the FDA was not available for two of the devices).

[190]*See supra* Part II. B.

[191]Mikael Gajecki et al., *Mobile Phone Brief Intervention Applications for Risky Alcohol Use Among University Students: A Randomized Controlled Study*, 9 ADDICTION SCI. & CLINICAL PRAC. (2014) (finding a smartphone app intended to reduce alcohol intake may have increased drinking among men).

[192]*See* Huguet et al., *supra* note 38.

[193]Nicholas et al., *supra* note 32, at 8.

a "virtual reality exposure therapy program, to be used in conjunction with pharmaceuticals."[194] Although this treatment approach may seem to mitigate the substitution problem, scientific evidence should confirm that the app's function does not negate or diminish the therapeutic effect of the pharmaceutical treatment.

The lack of clinical validation may also lead to the distribution of apps that follow principles that have been widely discredited by health care professionals. Conversion therapy, also known as sexual orientation change efforts (SOCE), has been widely discredited by health care professionals, and there is evidence to suggest it leads to harms such as depression, substance abuse, and suicide.[195] However, groups have published apps for conversion therapy.[196] The SOCE example is particularly egregious and companies are likely to remove these materials from their online stores,[197] but it is not difficult to imagine digital psychiatric therapies that follow other discredited practices. Those practices may not have the prominence of SOCE and therefore may escape attention and inflict harm on patients.

Moreover, although a particular software treatment may not present a high risk of bodily harm, there is a risk it could defraud customers through false scientific claims. Critics frequently cite the brain training industry as an example of this practice.[198] This kind of false advertising likely falls under FTC's jurisdiction. Without consistent enforcement against rigorous standards of safety and effectiveness, these MMAs may proliferate, making it more difficult for consumers and physicians to determine what therapies are appropriate. Given the importance of generating data on effectiveness, the possible safety of digital psychiatric therapies does not alone provide a rationale to avoid premarket regulation.

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[194]PEAR THERAPEUTICS, *supra* note 60.

[195]*E.g.*, *Resolution on Appropriate Affirmative Responses to Sexual Orientation Distress and Change Efforts*, AM. PSYCHOLOGICAL ASS'N, http://www.apa.org/about/policy/sexual-orientation.aspx [https://perma.cc/23W5-UKTL] (last visited Sept. 26, 2017); *Insufficient Evidence that Sexual Orientation Change Efforts Work, Says APA*, AM. PSYCHOLOGICAL ASS'N (Aug. 5, 2009), http://www.apa.org/news/press/releases/2009/08/therapeutic.aspx [https://perma.cc/B2U3-WP2H]; *The Lies and Dangers of Efforts to Change Sexual Orientation or Gender Identity*, HUM. RIGHTS CAMPAIGN, http://www.hrc.org/resources/the-lies-and-dangers-of-reparative-therapy [https://perma.cc/7B4P-2JG7**]** (last visited Sept. 26, 2017).

[196]*See, e.g.*, Cavan Sieczkowski, *'Gay Cure' App Claims To Help Users Find 'Freedom from the Bondage of Homosexuality'*, HUFFINGTON POST (May 31, 2013), http://www.huffingtonpost.com/2013/05/31/gay-cure-app_n_3365681.html [https://perma.cc/KBX8-EL9N]; Alex Spillius, *Apple under Fire for 'Gay Conversion' App*, TELEGRAPH (Mar. 20, 2011), http://www.telegraph.co.uk/technology/apple/8393974/Apple-under-fire-for-gay-conversion-app.html [https://perma.cc/X7TN-6BSY].

[197]The FDA may be reluctant to act in this area since SOCE is a topic that frequently leads to First Amendment litigation. However, constitutional challenges to state laws that ban SOCE have so far been unsuccessful. *See* Pickup v. Brown, 728 F.3d 1042 (9th Cir. 2013) (upholding California law that prohibits licensed mental health providers from providing SOCE therapy to minors), *aff'd, remanded, and reh'g denied*, 740 F.3d 1208 (9th Cir. 2014); King v. Governor of N.J., 767 F.3d 216 (3d Cir. 2014) (upholding New Jersey ban on conversion therapy). First Amendment challenges to laws and regulations viewed as restricting the freedom of speech of professionals are likely to continue. *See* Theodore T. Lee & Gregory D. Curfman, *Physician Speech and Firearm Safety:* Wollschlaeger v. Governor, Florida, 177 JAMA INTERNAL MED. 1189 (2017). However, regulatory action prohibiting MMAs that rely on discredited psychiatric practices may be less likely to attract litigation.

[198]*See* Gareth Cook, *Brain Games Are Bogus*, NEW YORKER (Apr. 5, 2013), http://www.newyorker.com/tech/elements/brain-games-are-bogus [https://perma.cc/9VJL-UU9J].

C. Digital Psychiatric Therapies and Other Software Treatments May Be Ineffective

FDA's current regulatory scheme does not adequately consider the importance of effectiveness for digital psychiatric therapies and other software treatments. This is a frequent critique of FDA's regulation of devices in general. A number of studies suggest that, in practice, sponsors do not adequately test high-risk devices because FDA is highly flexible in the evidence it considers for devices to meet the "reasonable assurance" standard required by the PMA process.[199]

However, it is not obvious what sort of effectiveness data should be required. Recent trends notwithstanding,[200] large, randomized, controlled trials are the norm for drugs. They are less prevalent in the device industry, however, resulting in less rigorous studies.[201] With regard to digital psychiatric therapies and other software-based devices, where FDA regulation and enforcement have been unclear, there has been little clinical study of device effectiveness.[202]

Another question is the comparison point for software treatments. One consideration is the digital placebo effect: the interaction with a digital interface may cause some people to report a positive benefit that is not attributable to the intervention itself.[203] In some cases, these therapies replace and/or complement drug-based regimens. To develop the most useful comparative effectiveness data, manufacturers should test digital psychiatric therapies and other software treatments against other available therapies as well as a digital placebo. Although detailed FDA guidance on trial design may be unnecessary for a company with expertise in navigating the regulatory process, many companies developing mobile health apps do not have experience navigating the regulatory process and may benefit from additional clarity.[204]

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[199]*E.g.*, Thomas B. Freeman et al., *Use of Placebo Surgery in Controlled Trials of a Cellular-Based Therapy for Parkinson's Disease*, 341 NEW ENG. J. MED. 988 (1999); Daniel B. Kramer et al., *Regulation of Medical Devices in the United States and European Union*, 366 NEW ENG. J. MED. 848 (2012); Benjamin N. Rome et al., *Approval of High-Risk Medical Devices in the US: Implications for Clinical Cardiology*, 16 CURRENT CARDIOLOGY REP. 489 (2014)*; see also* Brennan, *supra* note 112 (98% approval rate in 2015 for PMA applications).

[200]*But see* Aaron S. Kesselheim & Jerry Avorn, *Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy*, 316 J. AM. MED. ASS'N. 2357 (2016); Mildred Solomon, *The FDA's Controversial Duchenne Drug Approval and the Moral Impulse To Rescue*, HEALTH AFF. BLOG (Oct. 25, 2016), http://healthaffairs.org/blog/2016/10/25/the-fdas-controversial-duchenne-drug-approval-and-the-moral-impulse-to-rescue/ [https://perma.cc/LK66-5KPZ] (analyzing the approval of a drug for a rare disease on the basis of data with "major flaws").

[201]Daniel B. Kramer et al., *Premarket Clinical Evaluation of Novel Cardiovascular Devices: Quality Analysis of Premarket Clinical Studies Submitted to the Food and Drug Administration 2000–2007*, 17 AM. J. THERAPEUTICS 2 (2010); Sanket S. Dhruva et al., *Strength of Study Evidence Examined by the FDA in Premarket Approval of Cardiovascular Devices*, 302 J. AM. MED. ASS'N. 2,679 (2009).

[202]*See supra* Part II. B.

[203]Anthes, *supra* note 26, at 22; *see also* John Torous & Joseph Firth, *The digital placebo effect: mobile mental health meets clinical psychiatry*, 3 LANCET PSYCHIATRY 100 (2016). For a brief discussion of the placebo effect in the medical-device context, see Megan S. Wright, *A Case for Randomized, Double-Blinded, Sham-Controlled Class III Medical Device Trials*, 34 YALE L. & POL'Y REV. 199, 201–203 (2016) (discussing the placebo effect generally).

[204]*See* McClurg, *supra* note 18.

In addition, the 510(k) clearance process raises doubts about device effectiveness both in general and as applied to software treatments. This process has been heavily criticized because it does not necessarily involve clinical testing.[205] One study traced the ancestry of metal-on-metal hip implants, which have high rates of revision surgery, illustrating how 510(k) clearances have been stacked upon one another.[206] As a result, an untested, newly marketed device can differ significantly from the original device that went through rigorous studies. As discussed above, it is unclear whether and how the 510(k) process would apply to software treatments. This distinction is important because, although FDA can require clinical studies for an individual device on a case-by-case basis, the PMA process carries a presumption that clinical studies will be required and the 510(k) pathway does not. Moreover, if new software treatments do not have to be tested, it raises the possibility that consumers and clinicians might not be able to differentiate between those therapies that are effective and those that bestow little to no clinical benefit.

D. Regulating Digital Psychiatric Therapies and Other Software Treatments May Stymie Innovation

Stringent safety and effectiveness standards for digital psychiatric therapies and other software treatments may raise barriers to entry for new firms and frustrate innovation. However, not all innovation is equally valuable. In general, small medical device companies (and biotechnology companies in the pharmaceutical industry) are less likely to have the capacity to navigate the regulatory requirements of FDA.[207] Accordingly, small companies that are successful are likely to have succeeded because of their employees' regulatory knowledge, such as prior experience with clinical trials.[208] Since not all small companies have the advantage of deep regulatory knowledge, innovative companies in the process of developing a product that may be commercially viable have filled the gap by collaborating with or being acquired by larger companies that have regulatory and marketing competencies.[209]

The most promising companies developing apps are likely to receive backing from investors and expand their reach. Large pharmaceutical and biotech companies are already collaborating with, or investing in, companies developing digital psychiatric therapies.[210] However, there are limits to the availability of investment capital.

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[205]INSTITUTE OF MEDICINE, MEDICAL DEVICES AND THE PUBLIC'S HEALTH: THE FDA 510(K) CLEARANCE PROCESS AT 35 YEARS (2011); Kramer et al., *supra* note 199; Diana Zuckerman et al., *Lack of Publicly Available Scientific Evidence on the Safety and Effectiveness of Implanted Medical Devices*, 174 JAMA INTERNAL MED. 1781 (2014).

[206]Ardaugh et al., *supra* note 145.

[207]Edward B. Roberts, *Technological Innovation and Medical Devices*, *in* NEW MEDICAL DEVICES: INVENTION, DEVELOPMENT, AND USE 35, 46 (Karen B. Ekelman ed., 1988) ("The small firm is frequently the early-stage innovator and is most jeopardized by the regulatory process."); *see also* CARPENTER, *supra* note **Error! Bookmark not defined.**, at 649 ("Advantages in regulation were . . . correlated with the size and age of the company. This fact imposed substantial limitations and disadvantages upon smaller, newer companies.").

[208]Aaron K. Chatterji, *Spawned with a Silver Spoon? Entrepreneurial Performance and Innovation in the Medical Device Industry*, 30 STRATEGIC MGMT. J. 185, 200 (2009).

[209]Roberts, *supra* note 207, at 46.

[210]AKILI, *supra* note 20 (listing Pfizer, Shire, Merck Ventures and Amgen among the company's partners); PEAR THERAPEUTICS, *supra* note 21 (listing Novartis among the company's partners); Rebecca Robbins, *Inside the Push To Get Doctors To Prescribe Video Games*, STAT (Nov. 5, 2015),

Emerging companies with promising products might choose not to compete due to regulatory requirements[211] or because investors have already committed their capital to existing companies.

The distribution of regulatory burdens and investor funds is particularly relevant to MMA companies. MMA companies are relatively small: 61 percent of mobile health companies employ fewer than 100 employees (40 percent employ 10 or fewer) and 62 percent had revenue of $10,000 or less in 2015.[212] Smaller device companies tend to generate the most important innovations during the early stages of the development of new technologies.[213] Because smaller companies are more likely to produce critical innovations, fewer small firms could mean fewer innovative treatments available to patients. However, not all new and innovative treatments will be safe and effective. Those treatments that are likely to be safe and effective may be able to find partners beyond traditional investors, such as health systems interested in clinical applications.[214] An effective regulatory framework would encourage high-value innovation while protecting patient safety.

IV. RECOMMENDATIONS

The federal government should design a regulatory framework that specifically applies to digital psychiatric therapies and other software devices intended to directly treat or mitigate the symptoms of a condition or disease. FDA should recognize that these types of software are inherently different from software that plays more of a support role, such as operating a device like a pacemaker. Although FDA cannot feasibly prepare guidance for every condition and anticipate all new devices, it can more clearly exercise jurisdiction over software products that make specific treatment or diagnostic claims and enforce the FDCA for these products. As Professor Cortez writes, "The role of regulators is to facilitate the benefits of new technologies and manage their risks. Doing so should support long-term markets for the technology, preserve consumer trust, and level the playing field among competitors."[215] The federal government and particularly FDA must therefore address the concerns identified with respect to regulatory uncertainty, safety and effectiveness standards, and innovation. Fulfilling the promise of accessible, effective mental health treatment will require FDA to take a more active role in regulating these devices.

I recommend FDA: (1) exercise clear oversight of software treatments; (2) set device clearance standards that promote the development of devices that will meaningfully improve patient health; and (3) exercise its enforcement authority consistently and rely on FTC only to address fraudulent products.

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https://www.statnews.com/2015/11/05/video-game-developers-covet-new-market-patients/ [https://perma.cc/R4CF-X3J4].

[211] *See* Letter from Access Integrity, *supra* note 19.

[212] RESEARCH2GUIDANCE, *supra* note 3, at 3.

[213] Roberts, *supra* note 207, at 42.

[214] Heather Mack, *In-depth: The Path to Market for Digital Tools for Mental Health and Neurological Conditions*, MOBIHEALTHNEWS (Mar. 17, 2017), http://www.mobihealthnews.com/content/depth-path-market-digital-tools-mental-health-and-neurological-conditions [https://perma.cc/Z2Y8-XV23].

[215] Cortez, *supra* note 4, at 1229.

A. FDA Should Explicitly Regulate Software Treatments

FDA has the authority to institute a regulatory framework that adequately addresses digital psychiatric therapies. A new regulatory framework, whether constructed through guidance or rulemaking, would clearly establish these devices as under the jurisdiction of FDA. FDA has the authority to regulate these devices and should do so explicitly. Although the 21st Century Cures Act may provide some grounds for challenging FDA's jurisdiction, digital psychiatric therapies and other software treatments remain within the scope of FDA regulation.[216]

It is critical that Congress maintain FDA's jurisdiction in this area. Stripping FDA of its jurisdiction over digital health, especially over software treatments, would remove any incentive for developers to provide reasonable assurances of safety and effectiveness and would remove patient health protections at a critical time in the development of new technologies.[217] FDA must be able to regulate software developers because they are the entities that can identify defects, correct malfunction, and produce valuable scientific data most efficiently.

Congress should also support this regulatory framework by providing additional resources to FDA. Today, FDA's jurisdiction covers products representing more than 20 percent of U.S. consumer spending.[218] However, increases in funding have not been commensurate with increases in responsibility, suggesting FDA may not have the resources necessary to ensure the safety and effectiveness of the products it regulates.[219] In particular, FDA resources have not grown to keep pace with the explosion of health technologies.[220] To ensure FDCA enforcement and help build technical expertise within the agency, Congress should increase the resources available to FDA for regulating MMAs. Additional resources could help FDA to promulgate a set of regulations that updates the agency's understanding of software and other digital devices.[221] FDA currently has no dedicated office or committee advising on mobile health issues. Proposals such as the creation of an FDA office of mobile health provide a viable starting point to building the expertise necessary to regulate emerging health technologies effectively.[222] As health care continues to transition to digital operations, additional access to expertise and the resources to build regulatory capacity are essential.

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[216]*See supra* Part III. D. i.

[217]Nathan G. Cortez et al., *FDA Regulation of Mobile Health Technologies*, 371 NEW ENG. J. MED. 372, 376 (2014).

[218]Sheri Walker & Clark Nardinelli, *Consumer Expenditure on FDA Regulated Products: 20 Cents of Every Dollar*, FOOD & DRUG ADMIN. (Nov. 1, 2016), http://blogs.fda.gov/fdavoice/index.php/2016/11/consumer-expenditure-on-fda-regulated-products-20-cents-of-every-dollar/ [https://perma.cc/P3NX-LA9X].

[219]Judith Alphonse et al., *The FDA Funding Crisis*, 30 J. PHARMACY TECH. 57, 57 (2014); Peter Barton Hutt, *The State of Science at the Food and Drug Administration*, 60 ADMIN. L. REV. 431, 432 (2008) ("The FDA has become a paradigmatic example of the 'hollow government' syndrome—an agency with expanded responsibilities, stagnant resources, and the consequent inability to implement or enforce its statutory mandates.").

[220]Cortez et al., *supra* note 217, at 377.

[221]*See* Cortez, *supra* note 17, at 449.

[222]*See, e.g.*, Health Care and Innovation and Marketplace Technologies Act of 2013, H.R. 2363, 113th Cong. (2013); Cortez et al., *supra* note 217; Scott D. Danzis & Christopher Pruitt, *Rethinking the FDA's Regulation of Mobile Medical Apps*, 9 SCITECH LAW. 426, 444 (2013).

B. FDA Should Incentivize Innovation Benefitting Patients by Setting Rigorous Safety and Effectiveness Standards

FDA should apply PMA or clearance requirements to ensure safety and set rigorous standards for effectiveness. In doing so, FDA would make a decision regarding the desired direction of innovation: the enforcement of appropriate safety and effectiveness standards would ensure the development of devices that provide meaningful benefits. By promulgating regulations that more explicitly state that digital psychiatric therapies and other treatment MMAs are new devices, FDA would have the legal authority to require PMA applications.[223] Given the importance of creating an incentive to generate scientific data for these therapies, when evaluating these applications FDA should request large, randomized, controlled trials using digital placebos[224] and (if applicable) other available therapies, including non-digital alternatives, as comparators. Though clinical studies may be too expensive for smaller companies to pursue on their own, these companies can collaborate with more established stakeholders such as academic medical centers, insurers, pharmaceutical companies, and venture capital firms. Moreover, raising the bar for clearance or approval will help ensure that only the most promising interventions will attempt to market as a device and engage in clinical study.

This regulatory scheme should also speak clearly to the applicability of the 510(k) process to digital psychiatric therapies. The 510(k) process may be appropriate in circumstances in which the change to clinical effectiveness is likely minor or is addressing a safety risk. Software developers constantly make changes to their products; cybersecurity improvements or minor updates to usability or user enjoyment should not trigger regulatory scrutiny. However, if a change extends the software to a new indication (e.g., the software was treating ADHD and will now treat autism) or the developer claims that the change will substantially change clinical effectiveness, premarket approval may be more appropriate.

Opponents may argue that this approach will hurt innovation by burdening smaller companies. However, by providing patients and physicians with a baseline level of confidence in these devices, FDA may actually promote growth in this market.[225] Clear rules for compliance may also reduce the burden on regulated firms by reducing uncertainty.[226] Moreover, FDA can mitigate some of the impact on innovation and competition by continuing its practice of not enforcing the FDCA against MMAs that do not make treatment claims. This approach would reduce regulation for some companies while preserving the proposed regulatory scheme for digital psychiatric therapies and other software treatments. By not requiring approval or clearance for MMAs that do not make treatment or diagnostic claims, FDA would continue to give companies the flexibility to adjust their marketing to bring products into compliance.

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[223]21 C.F.R. § 860.134(a) (2016). These devices would be presumptively Class III devices assuming that the FDA does not grant *de novo* reclassification.

[224]*See* Anthes, *supra* note 26, at 21–22.

[225]*See* Daniel Carpenter, *Confidence Games: How Does Regulation Constitute Markets?*, *in* GOVERNMENT AND MARKETS: TOWARD A NEW THEORY OF REGULATION 164 (Edward J. Balleisen & David A. Moss eds., 2010) (arguing that the FDA's exercise of its gatekeeping authority catalyzes certain markets rather than burdening them by increasing experimentation and giving consumers confidence in the quality of the products).

[226]*See* Letter from Thompson on behalf of mHealth Regulatory Coalition, *supra* note 31.

Developers of digital psychiatric therapies that fail rigorous scientific trials (or are likely to do so) for treatment claims could market as low-risk wellness devices or otherwise escape FDCA enforcement (as developers are able to do now).

Commentators concerned about the burdens imposed on companies and FDA by the PMA process may advocate for expanded use of de novo clearances. For low- to moderate-risk devices, the PMA process may not provide additional benefits while imposing significant costs. The de novo clearance process is likely appropriate when the software treatment at issue is unlikely to impose a significant safety risk (e.g., it is used to supplement rather than replace the existing standard of treatment).[227] However, when a developer claims a software treatment addresses a disease or condition on its own, the software treatment raises significant safety issues that make it more risky.[228] In these instances, the PMA process is presumptively more appropriate for two main reasons.

First, it incentivizes the production of data critical to evaluating the device. Although FDA can require clinical studies on a case-by-case basis, the PMA process imposes a systematic presumption towards the production of clinical data. General clinical data requirements will help regulators, physicians, and patients understand software treatments at this early stage of development while allowing devices that do not make treatment claims to avoid regulation.

Second, the de novo pathway may fail to ensure the safety and effectiveness of follow-on devices. FDA may underestimate the risk of devices and not require evidence of safety and effectiveness when it should. Although FDA has issued several high-risk recalls due to software problems over the past few years, FDA did not initially classify these devices as high risk during the review process. [229] The authors of a study of software-related recalls could not confirm that manufacturers provided clinical data about any of the devices subject to high-risk recall (all but one went through the 510(k) process and the last was exempt from regulatory review).[230] More rigorous approval processes may have helped avoid these recalls, and a PMA default rule would ensure the production of clinical evidence. Moreover, once FDA clears a device through the de novo review pathway, manufacturers can obtain marketing clearance for "substantially equivalent" devices through the 510(k) pathway. This process for follow-on devices puts pressure on the adequacy of the 510(k) pathway, which many believe has failed to ensure the safety and effectiveness of devices cleared through the pathway.[231]

Congress can support FDA's regulations by considering whether the limitations of the existing regulatory framework are partially the result of an outdated statutory framework.[232] The FDCA's emphasis on risk for medical devices makes it more difficult for FDA to regulate new technologies that do not pose an obvious threat to

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[227]The reSET device is a good example of a software treatment used as a supplement since it "is intended to be used in conjunction with outpatient therapy and in addition to a contingency management system, a widely-used program for treating SUD that uses a series of incentives to reward patients for adherence to their treatment program." FOOD & DRUG ADMIN., *supra* note 11.

[228]See *supra* Part IV. B.

[229]Ronquillo & Zuckerman, *supra* note 144, at 547.

[230]*Id*. at 542 (finding that nonclinical studies were available for ten of the devices and information about the evidence before the FDA was not available for two of the devices).

[231]*See supra* Parts IV. A and IV. C.

[232]Cortez, *supra* note 17, at 449.

safety. The existing formulation of effectiveness, which merely balances risks against benefits, fails to ensure that devices are actually effective and rigorously tested. This burden of proof is too low in many contexts. For example, the 510(k) substantial equivalence test does not adequately ensure MMAs will perform like previous products, yet frequently updated software may also trigger unnecessary submissions. However, given the changes enacted by the 21st Century Cures Act, these broader reforms to the device process may not be politically viable at this time.

C. FDA Should Exercise its Enforcement Authority Consistently and Rely on FTC Only to Address Fraudulent Claims

In order to create a reliable market for safe and effective digital psychiatric therapies, FDA must exercise its enforcement consistently.[233] FDA's current case-by-case approach is inadequate to handle the wide range of digital psychiatric therapies on the market; it must exercise its authority to require PMA applications and enforce the requirements of the FDCA against digital psychiatric therapies and other treatment MMAs. Although it is possible to write some treatment claims to avoid FDA jurisdiction,[234] many MMAs currently fall under FDA's jurisdiction as written. Because FDA has not clearly announced its intention to enforce the FDCA against these products and engaged in more consistent enforcement action, developers of software treatments have continued to market their products. These developers may believe that they fall into categories subject to enforcement discretion described in FDA guidance. However, FDA should scrutinize developers' marketing claims and take action when they cross into disease-specific treatment claims.

It is notable that FTC has led some of the most prominent federal enforcement actions against software treatments (e.g., the Lumosity case).[235] However, FTC cannot be the primary enforcement agency of the basic requirements of the FDCA. The FDCA does not fall under FTC's jurisdiction. Practically, FTC cannot serve a gatekeeper role and is most likely to address software treatments after they are available to consumers. FTC also has less scientific expertise than FDA. FTC is therefore best equipped to address bad actors who make claims that are scientifically invalid to the point of fraud. FDA should therefore primarily rely on FTC for this function rather than ensuring safety and effectiveness.

CONCLUSION

Digital psychiatric therapies represent an exciting innovation that could transform the lives of people suffering from a variety of mental illnesses and conditions. However, the existing regulatory scheme creates uncertainty regarding enforcement, which may make it more difficult for companies to develop these products and bring them to market. Existing regulation also raises the possibility that marketed devices will not be effective enough to realize the promise of these therapies. Critics (sometimes incorrectly) charge the federal government and FDA with not keeping

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[233] *Id.* at 453 ("The final component of successful software regulation is consistent enforcement . . . . Without real enforcement, we risk having a lemons market like the dietary supplement industry, in which most products are ineffective, unsafe, or both.").

[234] *See supra* Part III. A.

[235] *See supra* Part III. D. ii.

pace with innovations in industry and technology.[236] This lag becomes more understandable in light of accelerating technological change, limited FDA resources, and statutory requirements that prioritize innovation without assurance that this innovation is valuable.[237]

To reduce the cloud of uncertainty under which developers of digital psychiatric therapies are operating, FDA and Congress must act to clarify the regulatory framework for devices targeting psychiatric conditions. To protect the public, the standards chosen should ensure digital psychiatric therapies are safe and effective.

[236]Cortez, *supra* note 4, at 1200 ("[C]ontrary to prevailing sentiment, Congress and federal regulators are facilitating rather than stifling mobile health technologies.).

[237]*See* Cortez, *supra* note 31; Hutt, *supra* note 219.