

Digital pills for the remote monitoring of medication intake: a stakeholder analysis and assessment of marketing approval and patent granting policies

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ABSTRACT

This article explores whether ‘digital pills’ that track medication intake should be used to enhance adherence. We concentrate on psychiatric conditions since these pose unique challenges. We analyze two public policies that potentially encourage the development of systems for remote monitoring of intake, namely the granting of patents and marketing authorization, and identify key stakeholders and their main interests so as to discuss whether these policies provide disproportionate benefits to some. The stakeholders identified are patients, system providers, drug manufacturers, insurers or healthcare systems, physicians, data users, and society at large. We discuss relevant industry reports, regulatory data, patent documents, and academic

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literature, and argue that there is concern that the drivers for these tracking systems are revenue and the monitoring of ‘compliance’ rather than ‘adherence.’ While accepting that the use of these systems can be justified in some circumstances, in our view these systems pose risks to patient autonomy, Shared Decision-Making, and privacy. We also find that policies on granting patents and marketing authorization overly favor the commercial actors and put patients’ interests at risk. Accordingly, we propose that additional safeguards are required.

KEYWORDS: adherence, compliance, digital pill, FDA, ingestible event marker, patents

I. INTRODUCTION

Incorrect taking of medication is widespread and can result in suboptimal health for the patient and, therefore, suffering for the patient and their caregivers. These problems are

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exacerbated in the case of persons with severe mental illness. ‘Digital pills’, which have a sensor embedded in a pill to track medication ingestion, claim to present one way to solve this problem.

In 2012, a California-based start-up, Proteus, was the first company ever to receive clearance from the US Food and Drug Administration (FDA) for such a sensor. A new regulatory category was created, the ‘Ingestible Event Marker’ (IEM), setting a precedent for the authorization of similar products. The idea, according to Proteus, was that their system would make unintentionally forgetful patients take better control and change their harmful habits and that physicians and caregivers would be given a tool to assist the patients in doing so.¹ Their business plan was to partner with pharmaceutical companies to license their IEM and co-develop a new product: a digital pill. Indeed, in 2017, the FDA gave its first approval to a ‘digital pill’ containing a drug together with the IEM to track ingestion and monitor drug dose regime adherence.² The decision set the precedent for similar products to be authorized in the future. The pill, trade name Abilify MyCite, is marketed by the company Otsuka Pharmaceutical Co. and contains the drug aripiprazole and an IEM from Proteus.

Aripiprazole is a widely prescribed antipsychotic drug, now generic, which first received FDA approval in 2002 and was until recently the highest revenue earning drug in the USA.³ Aripiprazole is usually prescribed for patients who may be vulnerable and who might require particular care. The new combination product, Abilify MyCite, is approved for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder, and for use as an add-on treatment for depression in adults. Following ingestion, the IEM generates a ‘signal’, which is detected by a patch worn on the patient’s chest and transmitted to a computing system via the patient’s mobile phone.⁴

Notably, in August 2020, Proteus went bankrupt as it struggled to find funding from investors. As part of the purchase agreement, Otsuka bought Proteus’ information technology assets, intellectual property, and equipment. On their website, we read ‘The purchase of Proteus assets and intellectual property will serve as a catalyst for implementing the next phase of our digital medicine program’.⁵ The reasons why Proteus went bankrupt, according to industry analysts,⁶ included concerns about the

1 Proteus Digital Health, *Proteus Announces Issuance of US Patent for Ingestible Digital Devices* (2011), <https://www.businesswire.com/news/home/20120130006675/en/Proteus-Announces-Issuance-of-U.S.-Patent-for-Digital-Health-Communications> (accessed Jan. 25, 2022).

2 For pills, the *consumption* of which is recorded by digital means, several terms have been proposed. However, we will use the term ‘digital pill’ for pills for which *ingestion* is recorded by such means. The terms ‘adherence’ and ‘compliance’ are both commonly used. We comment on the conceptual debates and controversies surrounding these terms (*infra* Section III).

3 See FDA, *Drugs@FDA: FDA Approved Drug Products* (2019), <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=207202/> (accessed Jan. 25, 2022); Nicholas J. Schork, *Personalized Medicine: Time for One-Person Trials*, 520 NATURE 609 (2015).

4 Such a system can of course alert the patient’s mobile phone when pill ingestion is due and record whether pill ingestion has taken place.

5 See Otsuka, *Otsuka America Pharmaceutical, Inc., Purchases the Assets of Proteus Digital Health, Inc.* Press release (2020), <https://www.otsuka-us.com/discover/proteus-assets-purchase> (accessed Jan. 27, 2022).

6 Angus Liu, *Otsuka Beats Back Novartis Opposition with \$15M Purchase of Smart Pill Developer Proteus* (2020), <https://www.fiercepharma.com/drug-delivery/otsuka-s-15m-purchase-smart-pill-developer-proteus-wins-court-backing-despite> (accessed Jan. 25, 2022).

cost of the pill. The cost of Abilify MyCite is \$1650 per month, while the generic, non-digital, equivalent costs far less.⁷ Moreover, as we discuss below (Section III), some patients had serious privacy concerns fueled by the vast amount of data collected by the sensor sent to a remote computer system operated by a for-profit company rather than directly to the patient's physician or caregiver. Finally, a 2019 study published in the BMJ argued that regulatory approval was based on weak evidence, and there was no evidence of better adherence to medication with the digital version of aripiprazole compared with the non-digital version.⁸

In December 2019, another company, EtectRx, received FDA 510(k) clearance for its ID-Cap System, a prescription ingestible system that sends adherence event logs to an external medical device.⁹ The 510(k) clearance procedure allows a company to compare a product to one that currently exists on the market, in other words to show that their product is substantially equivalent to a legally marketed device. EtectRx compared its product to Proteus' sensors, which, as discussed above, had already established a new regulatory category of products, the IEM.

The ID-Cap made by EtectRx is a standard capsule with a built-in ingestible sensor that transmits data once it is being dissolved by stomach fluid.¹⁰ A key difference according to the company is that there is no need for a patch; their reader can be worn as a pendant that hangs down to the abdomen and detects a signal received when the patient takes their medication. It communicates via Bluetooth with a smartphone app, which transmits data (related to adherence) to a secure provider web portal.¹¹ Another important difference with the Proteus system for the FDA was that the EtectRx device would not capture physiological metrics, and patients could choose to take off the device.¹² In this case, they may not put it back either because they decided not to or because they forgot to wear it. This, of course, is equally the case for Proteus' patch.

Like Proteus, EtectRx is looking to develop partnerships with pharmaceutical companies, and crucially, they will need to secure patients' trust, keep costs low, and amass evidence about what their technology can really do. Unsurprisingly, on February 26, 2021, EtectRx announced partnerships to evaluate patient acceptability of the digital pill ID-Cap. Their partner, Local Health (a pharmacy based in Chicago), will recruit patients, dispense the digital pill system, collect data, and publish survey results. The study focuses on mental health medication. They are trying to amass evidence to convince payers and patients, since there is little evidence of patient acceptance, and

7 Lisa Cosgrove et al., *Digital Aripiprazole or Digital Evergreening? A Systematic Review of the Evidence and Its Dissemination in the Scientific Literature and in the Media*, 24 BMJ EVID. BASED MED. 231 (2019).

8 *Id.*

9 FDA, *Letter from FDA to EtectRx* (2019), https://www.accessdata.fda.gov/cdrh_docs/pdf18/K183052.pdf (accessed Jan. 27, 2022).

10 Like Proteus, EtectRx has applied for and been granted US patents for its system (eg Neil R. Euliano, Brent A. Myers, Jose C. Principe, Venkata V. Meka & Glen Flores, *Electronic Medication Compliance Monitoring System and Associated Methods*, U.S. Patent No. 9,743,880 (filed Jun. 1, 2015) and Neil R. Euliano, Brent A. Myers, Jose C. Principe, Venkata V. Meka & Glen Flores, *Electronic Medication Compliance Monitoring System and Associated Methods*, U.S. Patent No. 10,292,642 (filed Aug. 25, 2017)). Since EtectRx's system involves a pendant rather than a patch, it is possible that the physiological parameters collectable by it may be somewhat more limited than is the case for the Proteus system.

11 FDA, *supra* note 9.

12 *Id.*

none demonstrating that these digital systems are better than simple interventions such as an alerting device.¹³

There are currently many companies active in the field of ingestible sensors, a market that is expected to boom with many more companies becoming involved, mainly in the USA and Japan. The COVID-19 pandemic has elevated the importance of telemedicine and a report by Market Research Future asserts that the ingestible sensor market is projected to grow phenomenally until 2027.¹⁴ New sensors are shaping the face of digital medicine, an emerging field of medicine that uses digital tools to promote the practice of medicine adopting a more individualized approach.¹⁵ Some commentators predict that a second generation of digital medicines will use Artificial Intelligence (AI) to mine data collected from a variety of sources, so as to inform personalized treatment plans, such as changing dosage, and encourage communication between patients and physicians to this effect.¹⁶ Control over data, costs, and patient acceptance will again loom large.

The analysis of this article focuses on digital pills that track medication intake and asks: should these devices be used to enhance medication adherence?¹⁷ We concentrate on psychiatric conditions since they pose unique challenges regarding non-intake of medication. To address our question, we adopt an ethical analysis of public policy, more specifically the public policies that ‘encourage’ the development and use of technologies for remote monitoring of medication intake by granting ‘patents’ and granting ‘marketing authorization’ for such technologies. Another reason why these policy domains are particularly interesting is that these are areas of regulation in which products and technologies are assessed on a ‘case-by-case’ basis, making them unique tools in the arena of technology regulation.

Whereas drug regulators such as the FDA focus on safety and efficacy, patent offices, such as the US Patent and Trademark Office (USPTO), have a different mandate. Governments entrust them with the task of assessing the patent eligibility, novelty, non-obviousness, and utility of the subject matter of the patent applications they receive. We would argue that, certainly when health-related products and technologies are at issue, these assessments are at least as important as decisions to grant or withhold marketing authorization. As noted by George Annas, patenting not only ‘adds another incentive to profit-making organizations to pursue certain lines of . . . experimentation’, but also ‘makes this pursuit seem more legitimate’.¹⁸

13 Andrea Martani et al., *Digital Pills: A Scoping Review of the Empirical Literature and Analysis of the Ethical Aspects*, 21 BMC MED. ETHICS art. n. 3 (2020).

14 MRF, *Ingestible Sensor Market Size to Reach USD 14,365.12 million by 2026 at 21.36% (2021)*, <https://www.globenewswire.com/news-release/2021/09/24/2302944/0/en/Ingestible-Sensor-Market-Size-to-Reach-USD-14-365-12-Million-by-2026-at-21-36-CAGR-Report-by-Market-Research-Future-MRFR.html> (accessed Jan. 25, 2022).

15 Eric Elenko et al., *Defining Digital Medicine*, 33 NAT. BIOTECHNOL. 456 (2015); Erratum at 34 NAT. BIOTECHNOL. 1206 (2016).

16 Yaron Ilan, *Improving Global Healthcare and Reducing Costs Using Second-Generation Artificial Intelligence-Based Digital Pills: A Market Disruptor*, 18 INT. J. ENVIRON. RES. PUBLIC HEALTH 811 (2021).

17 We should note at the outset, though, that some of the concerns and potential harms that we will discuss in this paper, for example those regarding data commercialization, are not specific to digital pills.

18 George Annas, *Hastings Center Report August 1987*, quoted in US Congress, Office of Technology Assessment, *New Developments in Biotechnology: Patenting Life—Special Report*, OTA-BA-370, 91 (1989).

The US patentability requirement of utility actually entails three kinds of ‘utility’. First, the invention must be usable (this is the requirement of ‘general utility’: the invention should be ‘operable or capable of any use’).¹⁹ Second, it should be possible to use the invention to achieve the purpose it was intended for: ‘It must operate to perform the functions and secure the result intended’.²⁰ This is the requirement of ‘specific utility’. Third, the invention should have a ‘beneficial utility’: its purpose should not be illegal, immoral, or contrary to ‘public policy’.²¹

With regard to the patentability requirement of ‘utility’ in the ‘specific context of inventions in the area of medicine’, Donald Chisum has noted that earlier legal decisions reflect the view that for inventions alleged to be useful for the treatment of a human disease, a more strict utility standard was necessary, hence the patent applicant needed to provide stronger ‘proof’ of the utility of the alleged invention.²² The underlying reasoning, according to Chisum, was that ‘[I]ssuance of a patent gave the drug or other medical invention an “appearance of authenticity,” an “oblique imprimatur of the Government” that might be used to mislead and deceive the consuming public’.²³

In *Isenstead v. Watson*,²⁴ for example, the District Court of the District of Columbia stated that:

Great care and scrutiny should be particularly taken in connection with applications for medical patents. While the granting of a patent does not legally constitute a certificate that the medicine to which it relates is a good medicine and will cure the disease or successfully make the test which it was intended to do, nevertheless, the granting of such a patent gives a kind of official imprimatur to the medicine in question on which as a moral matter some members of the public are likely to rely.²⁵

However, in 1906, the US ‘Federal Food & Drugs Act’ was enacted, which created the FDA. This had a significant impact on the role of the USPTO:

Although the early FDA had little actual regulatory authority, its creation signaled the eventual demise of the ‘beneficial utility’ standard for medical patents. With the FDA’s special expertise in ensuring the safety and efficacy of medicines, the PTO’s role as guarantor of the efficacy of patented devices and processes could be, and eventually was, limited.²⁶

Regardless of whether one thinks that limiting the role of the USPTO in this way was a good thing or not, given that patents provide a crucial incentive to invest both in and by R&D-based players, and therefore have a significant impact on whether invention is

19 ROBERT P. MERGES, *PATENT LAW AND POLICY. CASES AND MATERIALS* 189 (2nd ed. 1997).

20 1 Donald S. Chisum, *Chisum on Patents. A Treatise on the Law of Patentability, Validity and Infringement* § 4.01, at 4-2–4-2.1. (1997).

21 *Id.* This requirement has some similarities with Art. 53(c) of the European Patent Convention.

22 Chisum, *supra* note 20, at § 4.04[2], 4–30.

23 *Id.*

24 *Isenstead v. Watson*, 157 F. Supp. 7, 115 USPQ408 (D.D.C. 1957).

25 Quoted in Chisum, *supra* note 20, at § 4.04[2], at 4–31.

26 Joseph M. Reisman, *Physicians and Surgeons as Inventors: Reconciling Medical Process Patents and Medical Ethics*, 10 HIGH TECHNOL. LAW J. 355, 380–81 (1995).

followed through to innovation, decisions on patentability in the area of technology we are concerned with are highly relevant to our analysis.

Harrington explains that ethical analysis of public policy aims at scrutinizing the tensions between governments' obligations to protect the public interest and the various competing interests of other stakeholders.²⁷ In this way, we can evaluate policy choices and consequences by scrutinizing the extent to which a certain course of action adopted by a government optimizes the balance of those interests or gives precedence to some interests at the expense of others. Following this type of analysis, we will identify key stakeholders and discuss the main interests that seem to be at stake for each of them,²⁸ with a view to discussing whether the regulatory policies on which we focus provide disproportionate benefits to certain stakeholders at the expense of others. The purpose of such an analysis is to consider whether policy changes may be needed.²⁹

Stakeholders can be defined as 'actors who have an interest in the issue under consideration, who are affected by the issue, or who—because of their position—have or could have an active or passive influence on the decision-making and implementation processes'.³⁰ To identify the stakeholders relevant to our topic of remote monitoring of medication intake in the context of psychiatric disorders and to identify their interests and how they try to influence policy, we analyzed policy reports, industry reports, regulatory data, and patent documents, and we reviewed the relevant academic literature on digital pills and other electronic technologies for remote monitoring of medication intake. Although as yet few academic scholars have investigated this topic, we have greatly benefited from their insights.³¹ Clearly, (psychiatric) patients are key stakeholders, yet they are not the only stakeholders involved. The other stakeholders we have identified are physicians, drug manufacturers, insurers or (national) healthcare systems, clinical trial investigators, monitoring system providers, data users, and society as a whole.

The digital pill systems promise to promote the involvement of patients in their own care, potentially leading to improved clinical outcomes and reduced healthcare

27 L. Katharine Harrington, *Ethics and Public Policy Analysis: Stakeholders' Interests and Regulatory Policy*, 15 J. BUS. ETHICS 373 (1996).

28 Zsuzsa Varvasovszky & Ruairi Brugha, *How to do (or not do)...A stakeholder Analysis*, 15 HEALTH POLICY PLAN 338 (2000).

29 Harrington, *supra* note 27; TOBIAS GÖSSLING, *CORPORATE SOCIAL RESPONSIBILITY AND BUSINESS PERFORMANCE: THEORIES AND EVIDENCE ABOUT ORGANIZATIONAL RESPONSIBILITY* (2011).

30 Varvasovszky & Brugha, *supra* note 28, at 341, quoted in Marysol A. Balane et al., *Enhancing the Use of Stakeholder Analysis for Policy Implementation Research: Towards a Novel Framing and Operationalised Measures*, 5 BMJ GLOB. HEALTH e002661, 1 (2020).

31 Danae Dotolo et al., *A Hard Pill to Swallow: Ethical Problems of Digital Medication*, 63 SOCIAL WORK 370–72 (2018); Craig M. Klugman et al., *The Ethics of Smart Pills and Self-Acting Devices: Autonomy, Truth-Telling, and Trust at the Dawn of Digital Medicine*, 18 AM. J. BIOETHICS 3 (2018); Cosgrove, *supra* note 7; Sara Gerke et al., *Ethical and Legal Issues of Ingestible Electronic Sensors*, 2 NAT. ELECTRON. 329 (2019); Imogen Goold, *Digital Tracking Medication: Big Promise or Big Brother?* 11 LAW INNOV. TECHNOL. 203 (2019); Martani et al., *supra* note 13; Inigo de Miguel Beriain & Marina Morla González, *'Digital Pills' for Mental Diseases: An Ethical and Social Analysis of the Issues Behind the Concept*, 7 J LAW BIOSCI. ISAA40 (2020).

costs.³² According to some commentators, this promise will be fulfilled by what they term the ‘second generation’ digital pills that propose to use AI to mine data from a variety of sources so as to help patients understand their usage habits but also to give feedback on the impact of the drug to the clinician, for example so as to adjust dosage.³³ The alleged benefits of these digital pills are linked to their supposedly ‘personalized’ approach:

To overcome the hurdle of biases induced by big data, these systems implement an $n = 1$ concept in a personalized therapeutic regimen. The focus of the algorithm is to improve the clinically meaningful outcome for an individual subject.³⁴

...

Contrary to the common scenario of payers and drug companies sitting on opposing sides, the digital pill encourages cooperation. In addition, it creates a market differentiator for drug manufacturers, enabling them to increase market share and product price due to the improved clinical effect of the drug. The increased savings to payers and institutions motivates them to support the use of the digital pill.³⁵

However, we will argue that judging what these systems can do for the patient needs to take into account the crucial difference between ‘adherence’ and ‘compliance’. Compliance implies ‘following doctor’s orders’ while non-compliance/non-adherence often represents a rational decision on the part of patients, determined by factors such as their views on medication-taking, their life circumstances and available resources, competing priorities, and the need for patients to assert their independence. Adherence to medication requires that decision is taken according to the Shared Decision-Making model involving patients and their doctors.³⁶ We will come back to this (Section III).

Based on a review of the patents and business models of companies that are directly relevant to our topic, we will argue that there is serious concern that the main reasons behind the design of these tracking systems are to increase revenue for the pharmaceutical and ancillary industries and to monitor ‘compliance’. With regard to the latter, we agree with Beriain and González that:

[I]n a world with digital pills, a cooperative attitude on the part of the patient is no longer necessary to obtain accurate knowledge of [medication intake]. It is enough for patients to agree to use the pills (or for the system to force them to adopt them) so that their physicians know perfectly [whether they have really taken the medication].³⁷

32 Ronen Rozenblum et al., *Patient-Centered Healthcare, Patient Engagement and Health Information Technology: The Perfect Storm*, in INFORMATION TECHNOLOGY FOR PATIENT EMPOWERMENT IN HEALTHCARE 3–22 (Maria Adela Grando, Ronen Rozenblum & David Bates, ed., 1st ed. 2015); Kristin L. Carman et al., *Patient and Family Engagement: A Framework for Understanding the Elements and Developing Interventions and Policies*, 32 HEALTH AFF. 223 (2013); Halsted Holman & Kate Lorig, *Patients as Partners in Managing Chronic Disease. Partnership Is a Prerequisite for Effective and Efficient Health Care*, 320 BMJ 526 (2000).

33 Ilan, *supra* note 16.

34 *Id.*, at 4.

35 *Id.*, at 7–8.

36 See, for example, A. M. Stiggelbout et al., *Shared Decision Making: Concepts, Evidence, and Practice*, 98 PATIENT EDUC. COUNS. 1172–79 (2015).

37 Beriain & González, *supra* note 31, at 5.

While in principle we accept that there are circumstances where the limitation of patient autonomy and privacy by such systems ‘can’ be justified, in our view these tracking systems pose serious risks of unacceptable damage to patient autonomy, Shared Decision-Making, and privacy. If a simple alerting device could achieve comparable results in forgetful patients ‘consenting’ to take the medication, these systems would therefore be disproportionate. In patients ‘not consenting’ to take the medication, and where a simple alerting system would thus be insufficient, these systems arguably act as a straightjacket to enforce compliance. We propose that additional safeguards need to be put in place and offer some reflections on the role of the proposed AI regulation in Europe.

II. ENCOURAGING THE DEVELOPMENT AND USE OF THE TECHNOLOGY BY GRANTING MARKETING AUTHORIZATION: THE INVOLVEMENT OF THE FDA

The Proteus IEM was approved by the FDA in 2012 under the ‘de novo’ pathway,³⁸ when Proteus, then a small California-based start-up company, received clearance for the ‘Proteus Personal Monitor Including Ingestible Event Marker’.³⁹ With the FDA approving the Proteus device, a new generic category of device, the ‘ingestible event marker’, was created with a Class II risk classification.⁴⁰

When in 2019, a second company, EtecrRx, received FDA 510(k) clearance for its ID-Cap System, a prescription ingestible system that sends adherence event logs to an external medical device, the FDA compared the ID-Cap System to Proteus’ ingestible sensor and concluded that the two systems were similar and that the ID-Cap System could be authorized as an IEM. A crucial difference with the Proteus system is that the EtecrRx system does not require a patch and, in the authorized form, does not apparently capture physiological metrics.⁴¹

The FDA noted in its report on Proteus’ device that the IEM would need to be prescribed. Regarding the patch, the FDA reported that it was a miniaturized, wearable, data logger for ambulatory recording of physiological and behavioral metrics including heart rate, activity, body angle, and time-stamped patient-logged events, including events signaled by swallowing the IEM, that enabled unattended data collection for clinical and research applications, and that it would store and wirelessly send data to a computer.⁴²

38 Section 510(k) of the US *Federal Food, Drug and Cosmetic Act*, 21 U.S.C., requires device manufacturers to notify the FDA of their intent to market a medical device at least 90 days in advance (Premarket Notification, PMN or 510(k)). This allows the FDA to determine whether the device is equivalent to a device already on the market (the US *Safe Medical Devices Amendments* of 1990 to 21 U.S.C. defines substantial equivalence with another device on the market). Although most devices are approved under the 510(k) program, where there is no such equivalence then, according to the US *Food and Drug Administration Safety and Innovation Act* (2012), devices may be approved under a direct *de novo* pathway permitting the classification of novel, low to moderate risk devices in Class I or II without having to submit a 510(k) notification.

39 FDA, *Drugs@FDA: FDA Approved Drug Products* (2019), <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021436/> (accessed Jan. 25, 2022).

40 FDA, *Letter from FDA to Proteus Biomedical Dated 20 July 2012*, https://www.accessdata.fda.gov/cdrh_docs/pdf11/K113070.pdf/ (accessed Jan. 25, 2022); FDA, *Evaluation of Automatic Class III Designation (de novo) for Proteus Personal Monitor Including Ingestion Event Marker* (2012), https://www.accessdata.fda.gov/cdrh_docs/reviews/K113070.pdf/ (accessed Jan. 25, 2022).

41 FDA, *supra* note 9, at 7.

42 FDA, *Evaluation of Automatic Class III Designation*, *supra* note 40.

In ‘stage two’ of the FDA approval, in 2015, Proteus received clearance under the 510(k) program for the Proteus Digital Health Feedback Device,⁴³ a system that consists of a wearable patch, an IEM, and a software application which records physiological and behavioral metrics that can be used for the purposes of both measuring and monitoring patient ‘adherence’, and as stated in their application to the FDA, ‘the technology can also be used when quantifiable analysis of such metrics is desirable’. In short, the 2015 approval was for an aid in *measuring patient ‘adherence’*.⁴⁴

‘Stage three’ of the FDA approval, the approval of Otsuka’s digital pill in 2017, was different in that this time an IEM was combined with an active drug (aripiprazole) in a pill so as to form a single product with the trade name Abilify MyCite, the first ‘digital pill’. Aripiprazole, sold by Otsuka Pharmaceutical Co. under the brand name Abilify, was a widely prescribed drug, which first received FDA approval as a new molecular entity back in 2002. Aripiprazole is known as an antipsychotic drug and works by helping to restore the balance of certain natural chemicals in the brain. Patents on this drug had expired in 2015. What was new about the product approved by the FDA in 2017 was that Proteus’ ingestible sensor was embedded in aripiprazole tablets. The new combination product is approved for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder, and for use as an add-on treatment for depression in adults. The ingestible sensor makes it possible to track drug ingestion and data from the sensor are transmitted to a mobile app. In this way, patients can keep track of ingestion and if they so wish they can allow caregivers and their physician to have access to the information. It was the first time that a regulatory body approved such a drug-device combination, thus the decision set a precedent for the approval of similar products.

Since the FDA approved the digital pill as a combination product (a drug-device combination) and as a ‘pharmaceutical’ based on its ‘primary mode of action’, it can be prescribed like any other drug. Importantly, for the purposes of the present analysis, the FDA stated that there was no evidence that the approved product actually ‘improved’ adherence. It was approved for ‘monitoring ingestion’—not for improving adherence or compliance.⁴⁵

The FDA is concerned with safety and efficacy. ‘Efficacy’ requires that the patch detects the signal from the IEM when it is ingested (and retransmits that signal in some manner). ‘Safety’ requires that the IEM does not generate or release unduly toxic substances. Thus, FDA approval of the IEM *as such* (a ‘medical device’) has no connection with the ‘purpose’ of the IEM of improving patient adherence or compliance. Cosgrove et al. reviewed the clinical trials’ evidence submitted to the FDA and found that there was neither evidence of improved adherence nor improvement of quality of life or reduction of symptoms.⁴⁶ No data were submitted from clinical trials comparing intake using the generic version of aripiprazole and the digital version of the drug. The

43 FDA, *Letter from FDA to Proteus Digital Health Dated 27 June 2015*, https://www.accessdata.fda.gov/cdrh_docs/pdf15/K150494.pdf/ (accessed Jan. 25, 2022).

44 *Id.* at 3.

45 FDA, *Center for Drugs Evaluation and Research—Application Number: 207202Orig1s000—Labeling (2017)*, at 3, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/207202Orig1s000Lb1.pdf/ (accessed Jan. 25, 2022).

46 Cosgrove et al., *supra* note 7.

clinical trials were conducted to check usability, tracking, and any adverse skin reactions to the patch.

It is also worth noting a more recent study by Martani et al. who reviewed a number of studies in which digital pills had been tested on patients.⁴⁷ They describe various serious limitations, for example one study describes that most of the enrolled patients with schizophrenia were male and Black and were rated as mildly ill and capable of using the smartphone. The authors also note that none of the studies compare the accuracy of digital pills with that of other traditional methods, such as pill counts or self-reporting. Another important finding is the absence of studies on specific age groups, given that, for example, young adults and adolescents have concerns that may differ from those of older persons.

In short, the FDA's clinical review states that while 'Abilify MyCite' successfully tracks drug intake, there is no evidence that it improves adherence. In fact, the FDA review states:

[If] the...system fails, patients will not incur additional risk; they will continue to receive the exact treatment benefits of aripiprazole tablets without tracking. If the system works as intended and the patient chooses to share the data with the HCP [health care providers], the drug ingestion data could potentially help guide the prescribing physician on treatment interventions.⁴⁸

The FDA is trying to create a space for pharmaceutical innovation for the next generation of care delivery and the approval seems to be in line with the spirit of its Digital Health Innovation action plan and reflects the FDA's interest in exploring technological possibilities for addressing the problem of patient 'non-adherence'.⁴⁹ However, Europe took a different approach. While the Proteus IEM has also received regulatory clearance in the EU in 2016 as a biomarker for measuring patient 'adherence' to medication in clinical trials,⁵⁰ the European Medicines Agency (EMA) expressed concerns and required more evidence when reviewing Abilify MyCite. As a result, in July 2020, the company withdrew its application. The EMA stated:

47 Martani et al., *supra* note 13.

48 FDA, *Drug Approval Package: Abilify Mycite. Summary Review* (2018), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/207202Orig1s000SumR.pdf (accessed Dec. 23, 2021).

49 See NATIONAL ACADEMIES OF SCIENCES, ENGINEERING, AND MEDICINE, PAIN MANAGEMENT AND THE OPIOID EPIDEMIC: BALANCING SOCIETAL AND INDIVIDUAL BENEFITS AND RISKS OF PRESCRIPTION OPIOID USE (2017), <https://www.nap.edu/read/24781/chapter/1/> (accessed Jan. 25, 2022); FDA, *Digital health innovation action plan* (2017), https://www.fda.gov/downloads/MedicalDevices/DigitalHealth/UCMS68735.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery/ (accessed Jan. 25, 2022). In a press release, Mitchell Mathis, Director of the Division of Psychiatry Products in the FDA's Center for Drug Evaluation and Research of the FDA, said that 'Being able to track ingestion of medications prescribed for mental illness may be useful for some patients...The FDA supports the development and use of new technology in prescription drugs. ...' (*Id.*).

50 EMA, *QUALIFICATION OPINION ON INGESTIBLE SENSOR SYSTEM FOR MEDICATION ADHERENCE AS BIOMARKER FOR MEASURING PATIENT ADHERENCE TO MEDICATION IN CLINICAL TRIALS* (2016), https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-opinion-ingestible-sensor-system-medication-adherence-biomarker-measuring-patient_en.pdf (accessed Jan. 25, 2022).

The Agency could not assess how well the tablet with the integrated sensor, the patch and the App work together as only limited aspects of usability and technical performance were investigated. There was not sufficient evidence that Abilify MyCite is able to reliably measure intake of the medicine in the target population. From a safety point of view, there is a risk the patient could take too many doses because the digital medicine system may not work reliably. In addition, the patch can cause skin and subcutaneous tissue reactions. Therefore, at the time of the withdrawal, the Agency's opinion was that the benefits of Abilify MyCite did not outweigh its risks.⁵¹

Thus, we see a different set of concerns in the EMA's decision, reflecting more broadly the interests of the patient. To this aspect, we will turn in the following section (Section III).

As we will explain below (Section IV), we strongly suspect that the digital pill is specifically designed to increase 'compliance' rather than adherence and note that, with Abilify MyCite, Otsuka chose to 'embed' the IEM rather than simply to co-encapsulate an IEM and a drug pill, as a patient might simply remove the drug pill from the capsule. The use of means to prevent a patient 'cheating' or 'gaming' the system is also shown in an AI-based system developed by the New York company AiCure, which relies on image analysis rather than an IEM embedded in the medication itself. The patient's mobile phone runs an app, which reminds the patient that she is due to take a pill and the patient uses her mobile phone to video herself swallowing the pill. The data are transmitted to AiCure's computing system.

AiCure claims that it addresses the major shortcoming of counseling, educational, text messages, and electronic monitoring approaches: that they do not 'verify' drug administration. The AiCure system has been registered with the FDA as a 510(k) class 1 exempt device (ie exempt from pre-market notification requirements as a 'low risk device') since it 'merely informs clinical decision-making'. AiCure claims on its website that its system has been validated for use in future trial design to minimize risk and improve efficiencies across the drug development pipeline,⁵² as it not only monitors whether or not participants follow a prescribed drug regimen but also performs early 'patient categorization' (ie it identifies who is or is not more likely not to follow a drug regimen).

AiCure claims to 'unlock unprecedented amounts of objective behavioral data that AiCure will store and analyze to identify trends, behaviors and patterns of each individual to provide insights into the patient's condition'. The results can allegedly be used 'to incentivize individuals and intervene in a timely manner—with the goal of improving health and trial outcomes, and reducing the costs of care and drug development'. The company holds itself out as 'a behavioral data analytics company'.⁵³ On its website, the

51 EMA, INTREKKING VAN DE AANVRAAG VAN EEN VERGUNNING VOOR HET IN DE HANDEL BRENGEN VAN ABILIFY MYCITE (ARIPRAZOL) EMA/390789/2020. EMEA/H/C/005062 (2016), https://www.ema.europa.eu/en/documents/medicine-qa/questions-answers-withdrawal-application-marketing-authorisation-abilify-mycite-ariprazole_nl.pdf (accessed Jan. 27, 2022).

52 AiCure, *AiCure in Final Stages of Phase II Clinical Trial for Schizophrenia* (2014), <https://aicure.com/news/aicure-in-final-stages-of-phase-ii-clinical-trial-for-schizophrenia/> (accessed Jan. 25, 2022).

53 AiCure, *NeuroBo Selects AiCure to Advance Pivotal Neuropathic Pain Clinical Trial* (2019), <https://aicure.com/news/neurobo-selects-aicure-advance-pivotal-neuropathic-pain-clinical-trial/> (accessed Jan. 25, 2022).

company acknowledges that it collects biometrics, images, voice recordings, and even internet traffic.⁵⁴

As Adam Hanina, AiCure's co-founder and former CEO, put it: 'At AiCure, we're committed to improving patients' health worldwide by leveraging innovative AI-enabled technology that sees, hears and understands behavior'.⁵⁵

Who would pay AiCure for this and why? This leads us to the question as to whether AiCure's system is 'proof against gaming by the patient'. Interestingly, AiCure itself has answered that question with its US patent application for a system to detect patient attempts to pretend to swallow the prescribed pill, US Patent No. 10116903,⁵⁶ directed to an image recognition system for determining whether the recorded video shows the patient only pretending to swallow the pill. However, the range of pill shapes and colors available are limited, and many generic pill forms are simply white and disc- or torpedo-like. Thus, the patient, seeking to game the AiCure system, could simply take another pill of the same form or marked with the same color. Something more game-proof was needed. Including the pill manufacturer's trade mark (as applied to the pill) was one option, but it is not proof against the production of counterfeit pills.

What we see is a US patent granted to AiCure for pills surface-marked with a complex pattern rather than a simple trade mark.⁵⁷ Mass production of fake tablets would be easily detectable, and the complex pattern could itself be registered as a trade mark (here remember that trade mark registrations can be renewed indefinitely) and licensed to the exclusive pharma licensee. Add to this the fact that the system can be set not to recognize 'trade marks' other than those of the exclusive licensee and you have a much better game-proof system for which royalties can be collected indefinitely.

III. THE PATIENT

As the representative of a patient advocacy group recently explained in an interview: 'My concern as an advocate is that many people with schizophrenia are low income and on Medicaid. Is there a cost-benefit analysis that would indicate...the increased cost would be worth it?'⁵⁸

The primary benefit to the patient is a *reminder*, which could also be provided by a simple alarm, or a 'nudge', and confirmation that a pill has been taken. The immediate downside is cost—as mentioned below, the pills cost many times more than the 'dumb' generic alternative, a point to which we will return (Section V). Additionally, a patient may be so reassured by the provision of such a system that she fails to be alert to the

54 AiCure. *Privacy Policy* (2019), <https://aicure.com/privacy-policy/> (accessed Jan. 25, 2022).

55 AiCure, *AiCure's Revenue Soars as It Bolsters Client List and Executive Team* (2018), <https://aicure.com/news/aicures-revenue-soars-bolsters-client-list-executive-team/> (accessed Jan. 25, 2022).

56 Adam Hanina, Lei Guan & Dehua Lai, *Apparatus and Method for Recognition of Suspicious Activities*, U.S. Patent No. 10,116,903 (filed Mar. 14, 2013).

57 Adam Hanina, Yaniv Ganon, Maurice Lepouttre & Christian Wolf, *Method and Apparatus for Fractal Multilayered Medication Identification, Authentication and Adherence Monitoring*, U.S. Patent No. 9,361,562 (filed Mar. 15, 2013).

58 Christopher Rowland, *This \$1650 Pill Will Tell Your Doctors Whether You've Taken It. Is It the Future of Medicine?* WASHINGTON POST, April 28, 2019, https://www.washingtonpost.com/business/economy/this-1650-pill-will-tell-your-doctors-whether-youve-taken-it-is-it-the-future-of-medicine/2019/04/28/393281b2-4c10-11e9-b79a-961983b7e0cd_story.html?noredirect=on&utm_term=.d6adcd445cdc/ (accessed Jan. 25, 2022).

possibility of it failing, for example as a result of her mobile phone failing to operate or as a result of some other system failure. In cases of failure, patients might skip medications if the device incorrectly suggests they were already taken, or overdose if the device did not correctly register medication already taken, a point addressed in the EMA's statement discussed in closing the previous section (Section II).

A separate set of issues, which has been widely discussed in the limited literature on digital pills, concerns the automatic collection and sharing of patients' data and how this may affect autonomy,⁵⁹ represent surveillance,⁶⁰ introduce coercion, and compromise privacy.⁶¹ Concerns from the perspective of the patient are also discussed by Klugman et al., pointing to problems with informed consent, therapeutic misconception, external influences on decision-making, confidentiality and privacy, and device dependability.⁶² Tomlinson, in response to Klugman et al., defends the right of the patient to refuse to take her medication, arguing that otherwise the patient loses the possibility to demonstrate her own responsibility and agency and to show her trustworthiness (since after all trust is involved on both sides of the physician–patient relationship).⁶³ Likewise, both Terrasse and Sisti, and Carter et al. suggest that Klugman et al. underestimate the coercive effects of such systems, particularly for patients who are medically underliterate, incarcerated, mentally handicapped, or substance-addicted.⁶⁴ The forthright comments made by readers of the *New York Times* and *Washington Post* articles by Belluck and Rowland clearly demonstrate that these concerns are felt by laypersons too.⁶⁵

Indeed, the required controls on digital pills must address patient autonomy concerns. We see three groups of patients: the competent, the incompetent, and the 'socially dangerous'.⁶⁶ In this regard, we should stress that an adult person must be

59 Lisa Rosenbaum, *Swallowing a Spy—The Potential Uses of Digital Adherence Monitoring*, 378 NEJM 101 (2018); Anna K. Swartz, *Smart Pills for Psychosis: The Tricky Ethical Challenges of Digital Medicine for Serious Mental Illness*, 18 AM. J. BIOETHICS 65 (2018); Gerke et al., *supra* note 31; Goold, *supra* note 31; Beriain & González, *supra* note 31; Martani et al., *supra* note 13.

60 Nicole Martinez-Martin & Danton Char, *Surveillance and Digital Health*, 18 AM. J. BIOETH., 67 (2018); Gerke et al., *supra* note 31.

61 Amelia R. Montgomery, *Just What the Doctor Ordered: Protecting Privacy Without Impeding Development of Digital Pills*, 19 JETLAW 147 (2016); Karsten Weber et al., *Digital Medicine, Cybersecurity, and Ethics: An Uneasy Relationship*, 18 AM. J. BIOETHICS 52 (2018); Gerke et al., *supra* note 31; Goold, *supra* note 31; Beriain & González, *supra* note 31; Martani et al., *supra* note 13.

62 Klugman et al., *supra*, note 31.

63 Tom Tomlinson, *Getting Off the Leash*, 18 AM. J. BIOETHICS 48 (2018).

64 Mélanie Terrasse & Dominic A. Sisti (2018). *Policing Compliance: Digital Medicine and Criminal Justice-Involved Persons*, 18 AM. J. BIOETHICS 57 (2018); Adrian Carter et al., *Surveillance Medicine in the Digital Era: Lessons From Addiction Treatment*, 18 AM. J. BIOETHICS 58 (2018).

65 Pam Belluck, *First Digital Pill Approved to Worries About Biomedical 'Big Brother'*, NYT, November 13, 2017, <https://www.nytimes.com/2017/11/13/health/digital-pill-fda.html#commentsContainer> (accessed Jan. 25, 2022); Rowland, *supra* note 58.

66 Moreover, with regard to the terms 'dangerous' and 'normal', we should mention that UK sociologist Nikolas Rose, an expert on the history and sociology of psychiatry, makes the crucial observation that the term 'normality' is performative: 'Clearly, normality—of what it is to be normal, to think of oneself as normal, to be considered as normal by others—leads to a set of rather profound questions. We should probably accept that normality, today, is best thought of as a term of ascription, as performative—that is to say, it is a term that is best understood in its uses. So rather than thinking of it as having some substantive meaning, we should always ask who defines who as normal in relation to what criteria, in what practices, and with what consequences' (NIKOLAS ROSE, *OUR PSYCHIATRIC FUTURE: THE POLITICS OF MENTAL HEALTH* 9

considered to be competent until proof to the contrary is provided. Although a psychiatric illness can impact on competence, there is no reason to presuppose that a person suffering from a psychiatric illness lacks decisional capacity. The assessment of legal competence needs to be done on a case-by-case basis by a preferably well-trained professional.⁶⁷ It is widely agreed that the assessment of decisional capacity in psychiatric patients is a complex matter, and, as yet, there is no consensus on how this should be operationalized and what the minimal standards should be. Capacity is context-dependent and the complexity of the context/decision will determine which and how criteria should be used in the evaluation. The possible impression that a person's decision seems irrational or unwise in the eyes of the assessor or of other people concerned should not be central to the assessment. Rather, a judgement on decisional capacity should be based on the quality of the process of decision-making and the values involved. In this regard, it should also be noted that (in)capacity is dynamic, task-specific, and not stable and unchangeable over time.⁶⁸

For some persons suffering from mental illness, certain kinds of compulsory treatment (including outside the hospital setting) might be legally permitted or required, although the ethical and legal debates on these issues continue to highlight many unresolved controversies.⁶⁹ Indeed, a fierce debate is ongoing regarding the United Nations Convention on the Rights of Persons with Disabilities (CRPD), which was adopted in 2006 and entered into force in 2008.⁷⁰ This Convention, rightly in our view, approaches compulsory treatment as a human rights issue. However, its Article 12 is controversial. The UN has set up a Committee⁷¹ to monitor the implementation

(2019)). When we refer to 'socially dangerous' we are referring to those individuals *whom some in society believe to be abnormal in dangerous ways*. Unfortunately, as noted by Liat Ben-Moshe: 'In the hegemonic discourse, "mental illness" is seen as analogous to danger...and therefore containment and segregation are legitimized, as those labeled as "mentally ill" are seen as posing "a danger to themselves or others"...creating moral panics around the figure of the mentally ill as dangerous, especially through a racialized and gendered prism...'; see LIAT BEN-MOSHE, *DECARCERATING DISABILITY. DEINSTITUTIONALIZATION AND PRISON ABOLITION* 65 (2020).

67 Paul S. Appelbaum, *Assessment of Patients' Competence to Consent to Treatment*, 357 N. ENGL. J. MED. 1834 (2007); Ron Berghmans et al., *Mental Capacity: In Search of Alternative Perspectives*, 12 HEALTH CARE ANAL. 251 (2004).

68 Berghmans et al., *supra* note 67; Elizabeth C. Thomas et al., *A Systematic Review of Shared Decision-Making Interventions for Service Users With Serious Mental Illnesses: State of the Science and Future Directions*, 72 PSYCHIATRIC SERV. 1288 (2021).

69 However, in this regard, we should note that some commentators, specifically discussing the Proteus system, seem to feel that this category may be extended so far as to include diabetics: '[C]ourt-mandated treatments...may be relevant in relation to a number of disorders. Primary among these will be medication for mental disorders that may be associated with behaviours the court considers likely to lead to offending. This might include schizophrenia, bipolar and other similar conditions, but also encompass disorders that may increase the likelihood of harm to others in different ways, such as epilepsy, hypoglycaemia and diabetes, which can require medical management to maintain fitness to drive', Goold, *supra* note 31, at 19–20.

70 UNITED NATIONS, *CONVENTION ON THE RIGHTS OF PERSONS WITH DISABILITIES* (2006). We thank one of the anonymous reviewers for highlighting the relevance of this debate for our paper. Most countries of the world (185 as of 12 June 2022; the US is an exception) have ratified this Convention, although several have recorded reservations that would negate the more restrictive aspects of Article 12.

71 Committee on the Rights of Persons with Disabilities. See, for example, its General Comment No. 1 on Article 12: Equal recognition before the law. CRPD/C/GC/1.2014.

of the CRPD, and according to this Committee, the Convention prohibits involuntary detention and involuntary treatment of persons with mental health disabilities.⁷²

It should also be stressed that, in the context of psychiatry, Black, Indigenous and People of Color (BIPOC) and disabled persons are particularly vulnerable to structural racism and discrimination. They are disproportionately affected by coercive mental health practices. Moreover, BIPOC persons are disproportionately constructed as pathological within the criminal justice system. In *Decarcerating Disability*, a recent book about the similarities between prisons, psychiatric facilities, and institutions for people with intellectual and developmental disability labels and the connections between movements advocating for deinstitutionalization and prison abolition, Liat Ben-Moshe argues that disability and madness are frequently seen as:

a deficit, something in need of correction, medically/psychiatrically or by the correction industry, but not as a nuanced identity from which to understand how to live differently, including reevaluating responses to harm and difference. This is not only a scholarly omission but also a real danger to the lives of those most marginalized....⁷³

Ben-Moshe also discusses the emergence of the ‘antipsychiatry’ movement and notes that, in this context, psychiatric drugs were/are sometimes described as ‘chemical straitjackets’ or ‘chemical incarceration’:

[T]he introduction, and enforcement, of psychiatric drugs acted as a form of literal (not figurative) chemical incarceration that enabled populations that were deemed dangerous to live outside of an institution. These forms of chemical incarceration do not signal the liberation of the mad but their increased surveillance by other means.⁷⁴

The issue of surveillance is particularly relevant with regard to the context of digital psychiatric drugs. With regard to coercion (‘incarceration’), Russo and Wooley argue that, while coercive practices such as restraint and seclusion are ‘the most tangible expressions of psychiatric violence’, the fact that ‘(forced) medicalization of social realities remains a main feature of current mental “health” provision is rarely being problematized’.⁷⁵ As we will discuss below (*infra* this Section), social realities such as poverty and deprivation are certainly major risk factors for several mental illnesses.

72 One of the Committee’s comments on Article 12 (paragraph 40 of General Comment No. 1) states that: ‘The denial of the legal capacity of persons with disabilities and their detention in institutions against their will, either without their consent or with the consent of a substitute decision-maker... constitutes arbitrary deprivation of liberty and violates articles 12 and 14 of the Convention’. For interesting comments on the strengths and weaknesses of the Convention, see, for example: Jasna Russo & Stephanie Wooley, *The Implementation of the Convention on the Rights of Persons with Disabilities: More Than Just Another Reform of Psychiatry*, 22 HEALTH HUMAN RIGHTS J. 151 (2020); George Szmukler, ‘Capacity’, ‘Best Interests’, ‘Will and Preferences’ and the UN Convention on the Rights of Persons with Disabilities, 18 WORLD PSYCHIATRY 34 (2019) (offering arguments to interpret the Convention as not entailing an absolute prohibition of involuntary interventions in psychiatry); and Paul S. Appelbaum, *Saving the UN Convention on the Rights of Persons with Disabilities—from itself*, 18 WORLD PSYCHIATRY 1 (2019).

73 Ben-Moshe, *supra* note 66, at 1.

74 Ben-Moshe, *supra* note 66, at 62.

75 Russo & Wooley, *supra* note 72, at 159.

These concerns are exacerbated in view of the numerous studies indicating that organized psychiatry suffers from racial bias in multiple respects.⁷⁶ Biases do not only occur in relation to ‘judgements’ about mental capacity,⁷⁷ but also with regard to ‘risk factors’ for some mental illnesses, ‘severity’ of illness, ‘access’ to mental healthcare, ‘quality’ of mental healthcare, ‘compulsory’ psychiatric hospitalization (for minors as well as adults), and ‘(over)diagnosis’. Let us take a brief look at some recent studies, published in prestigious psychiatric journals, highlighting such biases.

On the basis of a recent review of research on the intergenerational impact of structural racism on depression, Hankerson and colleagues conclude that understanding risk factors for depression requires accounting for structural racism that is routinely experienced by racially and ethnically minoritized individuals.⁷⁸

Having reviewed research on mental health disparities, Barksdale and colleagues report that findings from community-based studies suggest that racial and ethnic minoritized adults have lower overall prevalence of mental disorders compared to White adults but that research suggests that, once diagnosed, racial/ethnic minoritized adults are more likely to have more severe and persistent courses of disorders than White adults. They conclude that one of the systemic factors driving these differences may be bias in diagnosis.⁷⁹

Alegria and colleagues, also on the basis of research reviewing scientific evidence regarding community mental health programs disparities, note that the time lag between seeking mental health services and actually receiving care is compounded for many people of color, ‘who are more likely than White people to have severe and persistent mental health conditions yet are less likely to access high-quality care’.⁸⁰ This is due to various factors, including cultural mistrust, racism, and discrimination from medical establishments, historical traumas and oppression, and underinsurance. Their review makes clear that:

research consistently demonstrates that Medicaid beneficiaries who are Black, Hispanic, American Indian, and Alaska Native experience, on average, poorer outcomes and more barriers to care compared to White beneficiaries’ and that ‘the quality of mental health care for marginalized individuals has not meaningfully improved in the past 20 years.’⁸¹

In relation to *compulsory admission to hospital, ie involuntary psychiatric detention*, too the disparities are striking. A recent systematic review and meta-analysis by Barnett and

76 In healthcare in general, racism constitutes a barrier towards achieving equitable healthcare. A recently published scoping review by Hamed and colleagues discusses abundant research showing unequal processes of delivering, accessing, and receiving healthcare across countries and healthcare indicators. See Sarah Hamed et al., *Racism in healthcare: A scoping review*, 22 BMC PUBLIC HEALTH 988 (2022). This review highlights, once again, that racialized minorities experience inadequate healthcare and being dismissed in healthcare interactions. Particularly relevant in relation to discussions on ‘adherence’ and ‘compliance’, research shows that these experiences are associated with lack of trust and delay in seeking healthcare (*Id.*).

77 We are grateful to one of the anonymous reviewers for emphasizing this crucial point.

78 Sidney H. Hankerson et al., *The Intergenerational Impact of Structural Racism and Cumulative Trauma on Depression*, 179 AM. J. PSYCHIATRY 434 (2022).

79 Crystal L. Barksdale et al., *Innovative Directions to Advance Mental Health Disparities Research*, 179 AM. J. PSYCHIATRY 397 (2022).

80 Margarita Alegria et al., *A New Agenda for Optimizing Investments in Community Mental Health and Reducing Disparities*, 179 AM. J. PSYCHIATRY 402 (2022).

81 *Id.* at 402.

colleagues, examining compulsory detention rates in Black, Asian, and minority ethnic and migrant groups in the UK and internationally, has found that Black Caribbean patients were significantly more likely to be compulsorily admitted to hospital than those in White ethnic groups. Black African patients also had significantly increased odds of being compulsorily admitted to hospital compared with White ethnic groups, as did, to a lesser extent, South Asian patients. Black Caribbean patients were also significantly more likely to be readmitted to hospital than White ethnic groups. Migrant groups were significantly more likely to be compulsorily admitted to hospital compared with native groups.⁸²

On the basis of retrospective data, Knight and colleagues specifically investigated whether Black patients with first-episode psychosis in Canada were at a 'higher risk for coercive referral and coercive intervention' than non-Black patients with first-episode psychosis. They found that Black persons of Caribbean or African descent with first-episode psychosis were significantly more likely to be coercively referred and coercively treated. They call for more research into the role of ethnoracial status in hospital admissions and the role of racial prejudices in the assessment of danger.⁸³

Furthermore, various researchers have found biases regarding both 'diagnosis' and 'treatment' of mental illnesses including schizophrenia and psychosis. For example, in the USA, Black men have been disproportionately diagnosed with schizophrenia.⁸⁴ Metz and Roberts discuss an emerging educational movement known as 'structural competency', which claims that:

many health-related factors previously attributed to culture or ethnicity also represent the downstream consequences of decisions about larger structural contexts, including health care and food delivery systems, zoning laws, local politics, urban and rural infrastructures, structural racisms, or even the very definitions of illness and health.⁸⁵

They illustrate this, *inter alia*, with a historical case study on the overdiagnosis of schizophrenia, explaining that the misdiagnosis of schizophrenia in Black men in the USA resulted not only from clinical bias but also from structural shifts in psychiatric definitions of this illness. The addition of components such as aggression and hostility to the definition in DSM-II had far-reaching racial implications.⁸⁶

Coleman and colleagues have studied racial-ethnic variation in diagnoses and treatment of mental disorders in adults in large not-for-profit healthcare systems in the USA. 'Receiving' a psychiatric diagnosis varied significantly by race-ethnicity. Native American/Alaskan Native patients had the highest rates of any diagnosis (20.6%) and Asians had the lowest rates (7.5%). As regards 'treatment', among patients with a

82 Phoebe Barnett et al., *Ethnic Variations in Compulsory Detention Under the Mental Health Act: A Systematic Review and Meta-analysis of International Data*, 6 LANCET PSYCHIATRY 305 (2019).

83 Sommer Knight et al., *Ethnoracial Differences in Coercive Referral and Intervention Among Patients With First-Episode Psychosis*, 73 PSYCHIATR SERV. 2 (2022).

84 Jonathan M. Metz & Dorothy E. Roberts, *Structural Competency Meets Structural Racism: Race, Politics, and the Structure of Medical Knowledge*, 16 VIRTUAL MENTOR—AMA J. ETHICS 674 (2014).

85 *Id.* at 674; see also Jonathan M. Metz & Helena Hansen, *Structural Competency: Theorizing a New Medical Engagement With Stigma and Inequality*, 103 SOC. SCI. MED. 126 (2014).

86 JONATHAN M. METZ, *THE PROTEST PSYCHOSIS: HOW SCHIZOPHRENIA BECAME A BLACK DISEASE* (2009).

psychiatric diagnosis, 73% received psychotropic ‘medication’. Non-Hispanic White patients were significantly more likely (77.8%) than other racial–ethnic groups to receive medication. In contrast, only 34% of patients with a psychiatric diagnosis received formal ‘psychotherapy’.⁸⁷

As mentioned earlier, the required controls on digital pills must address patient autonomy concerns. For competent patients, what is necessary is real informed consent⁸⁸ and the availability of the option to refuse the digital pill or to choose a normal generic equivalent without fear of punishment by way of refusal of insurance or treatment. Insurers might withdraw healthcare cover unless the patient ‘consents’ to using the system or to taking the medication under supervision or in a depot form. It might become difficult to find physicians who will not use such a system (as insurers might refuse to accredit them).

Beyond these important considerations, there is another important concern that we would like to discuss: digital pills do not in fact address the key factors behind the lack of adherence to medication for psychiatric patients. First of all, as we already noted in Section I, incorrect taking of medication can result in suboptimal health for the patient, even risking (re-)hospitalization and death, and, as a consequence, suffering for the patient and her caregivers. Moreover, medical costs borne by the patients, their families, their insurers, or their healthcare systems may increase. Thus, in principle, improving correct intake of medication is clearly a desirable goal.

In psychiatric disorders, in particular, incorrect medication intake arises from a complex interplay between ‘personal factors’ (eg individual values and illness beliefs, prior experiences with illness and treatment, personality, insight, cognitive abilities, financial means, and social support), ‘illness-related factors’ (eg specific symptoms, positive aspects of the illness, failure to improve, cognitive impairment, and lack of motivation), and ‘treatment-related factors’ (eg therapeutic alliance with the physician and the treatment team, therapeutic setting, adequate information, non-conflicting advice, effectiveness, treatment complexity, side-effects, and stigma).⁸⁹ The occurrence of incorrect medication intake is similar to that in non-psychiatric populations.

The key consequences of incorrect medication intake in people with severe mental illness are partial response to treatment, greater risk of relapse and rehospitalization, suicide, and poor global outcomes.⁹⁰ Obviously, these conclusions from the literature are dependent on the actual efficacy of a specific pharmacological intervention for a specific disorder. Let us therefore take a closer look at schizophrenia, bipolar disorder, and depression, the conditions for which aripiprazole is usually prescribed.

87 Karen J. Coleman et al., *Racial-Ethnic Differences in Psychiatric Diagnoses and Treatment Across 11 Health Care Systems in the Mental Health Research Network*, 67 *PSYCHIATR. SERV.* 749 (2016).

88 See Beriaín & González, *supra* note 31 for a detailed analysis on the requirements of consent so that patients make an optimally autonomous choice.

89 Francisco J. Acosta et al., *Medication Adherence in Schizophrenia*, 2 *WORLD J. PSYCHIATRY* 74 (2012); Sainza García et al., *Adherence to Antipsychotic Medication in Bipolar Disorder and Schizophrenic Patients: A Systematic Review*, 36 *J. CLIN. PSYCHOPHARMACOL.* 355 (2016); Kyoko Higashi et al., *Medication Adherence in Schizophrenia: Factors Influencing Adherence and Consequences of Nonadherence, a Systematic Literature Review*, 3 *THER. ADV. PSYCHOPHARMACOL.* 200 (2013); Julie Kreyenbuhl et al., *A Review of Behavioural Tailoring Strategies for Improving Medication Adherence in Serious Mental Illness*, 18 *DIALOGUES CLIN. NEUROSCI.* 191 (2016).

90 García et al., *supra* note 92; Higashi et al., *supra*, note 92; Kreyenbuhl et al., *supra*, note 92.

In patients with ‘schizophrenia’, the efficacy of antipsychotic agents in the treatment of acute psychotic episodes has been well established for many decades and remains confirmed in the most recent meta-analysis of acute RCTs.⁹¹ For most patients, long-term treatment with antipsychotics is effective in the prevention of relapse.⁹² Schizophrenia patients inclined to take their medication correctly are less symptomatic and have better overall outcomes and a lower suicide risk.

Psychotic symptoms in ‘bipolar disorder’ also respond well to antipsychotic agents, while some antipsychotics also exert mood-stabilizing properties useful in the long-term maintenance treatment of the disorder.⁹³

In ‘depression’, the main pharmacological treatment is with antidepressants. The efficacy of antidepressants is mainly established for severe depression and less clear for mild-to-moderate depression.⁹⁴ The evidence of efficacy of antipsychotics in the treatment of depression is much less convincing. The effects in acute depression are only moderate.⁹⁵ Antipsychotics as adjuvant treatment may be beneficial when used short term in patients with treatment-resistant depression who have specific symptoms (severe ruminations, melancholia, major sleep disturbance), but there is no support for long-term use.⁹⁶

In patients with ‘schizophrenia’, the key drivers of incorrect medication intake are lack of insight, medication beliefs, and substance abuse. Factors positively influencing correct medication intake are a good therapeutic relationship, the perception of benefits of treatment, and the presence of limited or no side effects of treatment.⁹⁷ In ‘bipolar disorder’ more complex medication regimes and side effect burden were also associ-

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- 91 Stefan Leucht et al., *Sixty Years of Placebo-Controlled Antipsychotic Drug Trials in Acute Schizophrenia: Systematic Review, Bayesian Meta-Analysis, and Meta-Regression of Efficacy Predictors*, 174 AM. J. PSYCHIATRY 927 (2017); Rajiv Tandon et al., *Schizophrenia, ‘Just the Facts’ 5. Treatment and Prevention. Past, Present, and Future*, 122 SCHIZOPHR. RES. 1 (2010); Maximilian Huhn et al., *Comparative Efficacy and Tolerability of 32 Oral Antipsychotics for the Acute Treatment of Adults with Multi-episode Schizophrenia: A Systematic Review and Network Meta-analysis*, 394 LANCET 939 (2019).
- 92 Marc De Hert et al., *The Use of Continuous Treatment Versus Placebo or Intermittent Treatment Strategies in Stabilized Patients with Schizophrenia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials with First- and Second-Generation Antipsychotics*, 29 CNS DRUGS, 637 (2015).
- 93 Jean-Michel Azorin & Nicolas Simon, *Dopamine Receptor Partial Agonists for the Treatment of Bipolar Disorder*, 79 DRUGS. 1657 (2019); Sameer Jauhar & Allan H. Young, *Controversies in Bipolar Disorder; Role of Second-Generation Antipsychotic for Maintenance Therapy*, 7 INT. J. BIPOLAR DISORD. 10 (2019).
- 94 Andrea Cipriani et al., *Comparative Efficacy and Acceptability of 21 Antidepressant Drugs for the Acute Treatment of Adults With Major Depressive Disorder: A Systematic Review and Network Meta-Analysis*, 391 LANCET 1357 (2018); Michael P. Hengartner & Martin Plödel, *Statistically Significant Antidepressant-Placebo Differences on Subjective Symptom-Rating Scales Do Not Prove That the Drugs Work: Effect Size and Method Bias Matter!*, 9 FRONT. PSYCHIATRY 517 (2018).
- 95 Laura Amato et al., *Systematic Review to Evaluate the Efficacy, Acceptability and Safety of Second-Generation Antipsychotics for the Treatment of Unipolar and Bipolar Depression*, 109 RECENTI PROG. MED. 474 (2018).
- 96 Roger Mulder et al., *Treating Depression With Adjunctive Antipsychotics*, 20(Suppl 2) BIPOLAR DISORD. 17 (2018).
- 97 Higashi et al., *supra* note 92; John M. Kane et al., *Non-adherence to Medication in Patients With Psychotic Disorders: Epidemiology, Contributing Factors and Management Strategies*, 12 WORLD PSYCHIATRY 216 (2013); Rosemarie McCabe et al., *The Therapeutic Relationship and Adherence to Antipsychotic Medication in Schizophrenia*, 7 PLOS ONE e36080 (2012); Kyra-Verena Sendt et al., *A Systematic Review of Factors Influencing Adherence to Antipsychotic Medication in Schizophrenia-Spectrum Disorders*, 225 PSYCHIATRY RES. 14 (2015).

ated with rates of incorrect medication intake.⁹⁸ In ‘depression’, Ho and colleagues confirmed the complex interplay between personal, illness, and treatment-related factors.⁹⁹ Major factors for poor medication intake in depression are duration and chronicity of the disorder, beliefs about depression, medical complications, side effects, poor quality of life, and poor treatment alliance.¹⁰⁰ In sum, ‘forgetfulness’ is not mentioned in these (meta-)reviews.

In the literature, a range of different terms is used to describe incorrect intake of medication by the patient. Conceptual controversies surround the terms ‘(non-)compliance’ and ‘(non-) adherence’, and we would argue that these controversies are highly relevant to an analysis of the implications of digital pills for patient autonomy. According to a frequently cited review article:

The word ‘adherence’ is preferred by many health care providers, because ‘compliance’ suggests that the patient is passively following the doctor’s orders and that the treatment plan is not based on a therapeutic alliance or contract established between the patient and the physician. Both terms are imperfect and uninformative descriptions of medication-taking behavior.¹⁰¹

Chakrabarti, a psychiatrist, explains that:

[T]he traditional medical model often assumes that any treatment based on scientific evidence is always in the best interests of the patient, and it would be unwise, or even irrational for the patient not to comply with the clinician’s suggestions regarding such treatment. Then again, according to social, cognitive and behavioural perspectives, non-compliance/non-adherence often represents a rational decision on part of patients, determined by factors such as their views on medication-taking, their life circumstances and available resources, competing priorities, the need for patients to assert their independence.¹⁰²

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- 98 Vicki C. Fung et al., *Complex Polypharmacy in Bipolar Disorder: Side Effect Burden, Adherence, and Response Predictors*, 257 J. AFFECT. DISORD. 17 (2019); García et al., *supra* note 92.
- 99 Siew Ch. Ho et al., *Barriers and Facilitators of Adherence to Antidepressants Among Outpatients With Major Depressive Disorder: A Qualitative Study*, 12 PLOS ONE. e0179290 (2017).
- 100 See Ho et al., *supra* note 102; Katelyn R. Keyloun et al., *Adherence and Persistence Across Antidepressant Therapeutic Classes: A Retrospective Claims Analysis Among Insured US Patients with Major Depressive Disorder (MDD)*, 31 CNS DRUGS 421 (2017); Pornchanok Srimongkon et al., *A systematic Review of Measures of Medication Adherence in Consumers With Unipolar Depression*, 15 RES. SOCIAL ADM. PHARM. 3 (2019). Apart from psychosocial and psychoeducational approaches, the best studied intervention to prevent poor oral medication intake in psychosis spectrum disorders and bipolar disorder is the use of depot or long-acting injectable antipsychotic (LAI) drugs. See Amanda Krogmann et al., *Keeping Up With the Therapeutic Advances in Schizophrenia: A Review of Novel and Emerging Pharmacological Entities*, 24(S1) CNS SPECTR. 38 (2019); Isabella Pacchiarotti et al., *Long-Acting Injectable Antipsychotics (LAIs) for Maintenance Treatment of Bipolar and Schizoaffective Disorders: A Systematic Review*, 29 EUR. NEUROPSYCHOPHARMACOL. 457 (2019); Takefumi Suzuki, *A Further Consideration on Long-Acting Injectable Versus Oral Antipsychotics in the Treatment of Schizophrenia: A Narrative Review and Critical Appraisal*, 13 EXPERT OPIN. DRUG DELIV. 253 (2016). In schizophrenia, non-randomized studies indicate that LAI drugs are more effective than oral medication to prevent the negative impact of relapse, but the results of RCTs are less impressive (Suzuki, *supra*). In patients with an affective component (bipolar or schizoaffective), LAI drugs mainly prevented manic episodes but not depressive recurrence (Pacchiarotti et al., *supra*).
- 101 Lars Osterberg & Terrence Blaschke, *Adherence to Medication*, 353 NEJM 487–97 (2005).
- 102 Subho Chakrabarti, *What’s in a Name? Compliance, Adherence and Concordance in Chronic Psychiatric Disorders*, 4 WORLD J. PSYCHIATRY 30, 31–2 (2014).

Chakrabarti further explains the key differences between the terms ‘compliance’ and ‘adherence’ as follows:

Compliance...was intended to be a neutral alternative to earlier descriptions of patients who did not follow the clinician’s advice, such as ‘untrustworthy’, ‘uncooperative’, or as proposed by Hippocrates, patients who lie about taking treatment.... [Compliance has become] synonymous with a paternalistic conceptualization of medication-taking behavior, which disregards patients’ perceptions on medication-taking.... The concept of adherence places emphasis on a process, in which the appropriate treatment is decided after discussion between the prescriber and the patient. It implies that the patient is under no compulsion to accept a particular treatment, and shall not be held solely responsible for the failure of a treatment plan because of non-adherence....¹⁰³

For the purposes of this paper, ‘adherence’ will be used to indicate that the decision to use the drug was taken in a truly Shared Decision-Making process between the patient or her representative and the healthcare professional.¹⁰⁴ By contrast, ‘compliance’ will be used when the decision to prescribe was taken solely by the healthcare professional, when the patient is not competent to take part in the decision-making, or when the correlation with the intended dosage is viewed from outside the physician–patient relationship, for example in clinical trials. The central thesis to this paper is that, while the rhetoric employed in support of the adoption of digital pills is that ‘adherence’ will be improved, the underlying drive for their adoption seems instead to be that ‘compliance’ can be achieved.

As noted by Rosenbaum, ‘the most effective adherence booster may be giving doctors and patients the time to explore the beliefs and attributions informing medication behaviors’.¹⁰⁵ Indeed, ‘adherence’ presumes that the patient has agreed and consented to take the medication because she understands the importance of that action to achieve health-related goals important to her, and that patient autonomy has thus been respected. This, of course, presupposes a good therapeutic relationship. In such circumstances, if the patient fails to actually take the drug, then this can only represent ‘non-adherence’ where the patient forgot or where external factors beyond the patient’s control prevented the drug from being taken.

A simple alerting system, for example an app on the patient’s mobile phone, would seem sufficient to prevent the problem arising from forgetfulness.¹⁰⁶ In these situations, tracking the actual drug intake is unnecessary, disproportionate, intrusive, and overly complex, and thus in principle inappropriate.

103 *Id.*, at 32–3.

104 Stiggelbout et al., *supra* note 36.

105 Rosenbaum, *supra* note 59, at 103.

106 Although the REMIND trial of Choudhry et al. found that providing patients with low-cost reminder devices such as pill containers with timers was not the answer to poor adherence, Kronish & Moise point out that other simple solutions *have* shown promise and so the simple should not simply be dismissed as ineffective. Niteesh K. Choudhry et al., *Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial. Full Coverage for Preventive Medications After Myocardial Infarction*, 365 *NEJM* 2088 (2011); Ian M. Kronish & Nathalie Moise, *In Search of a ‘Magic Pill’ for Medication Nonadherence*, 177(5) *JAMA INTERN. MED.* 631 (2017). See also Ramnath Subbaraman et al., *Digital Adherence Technologies for the Management of Tuberculosis Therapy: Mapping the Landscape and Research Priorities*, 3 *BMJ GLOB. HEALTH* e001018 (2018).

Sensor companies seem to have taken notice of patient dissatisfaction. The business plan of EtectRx, the company that makes the ID-Cap mentioned *supra* (Section I), is worth noting. In January 2021, they announced a partnership with Pear Therapeutics, a company that makes mobile applications that deliver therapy sessions (encouraging patients to answer questionnaires and filling self-reports). These apps, termed ‘digital therapeutics’, may receive authorization by the FDA, and if they do, they will need to be prescribed and reimbursed. Pear Therapeutics has successfully gained authorization for three of its ‘digital therapeutics’ through the FDA authorization process (for opioid use disorder, substance use disorder, and insomnia treatment) and they are now preparing a new one for alcohol use disorder. The two companies (Pear and EtectRx) will combine medication ‘adherence’ data with digital therapeutics, and it seems that a new design for digital pills is emerging, based on the idea of self-management. In this case, the (ingestible) sensor and the app will still need to be combined with a pharmaceutical product. Valerie Sullivan, former CEO of EtectRx, said in an interview:

I had thought it might be a good idea to partner with a digital therapeutic to see if they could integrate our confirmation of ingestion of a medication into their app so patients could see: ‘This is how I’m feeling, and this is what’s happening to me right now, and this is when I took my medicine, not when I entered in when I took my medicine, but actually when a digital pill detected it’. I love the idea of having the power for patients to treat themselves and analyze their behaviors.¹⁰⁷

The two companies are exploring how a co-developed product could help ‘optimize dosage’. If they can do this, then they can claim the improvement of a clinical outcome for a particular person.

Questions regarding data control are still unclear but of paramount importance in such a model. One of us has argued elsewhere that the best solution would be to give patients control over the data (reference blinded for review) but this is a hotly debated issue, whose way of resolving will determine how the field will evolve in the future. As regards patient autonomy, it remains to be seen whether patients will freely enter data (with regard to adherence or the lack thereof) and freely consent to allow an algorithm to mine the data, make recommendations, and communicate information to caregivers. For such a scheme to work, rather than being asked to ‘act on data’ to ‘treat themselves and analyze their behavior’, these tools should be companions¹⁰⁸ that furnish information to be discussed further in the context of a therapeutic relationship. If digital pills transform into an e-health tool (with patients completing questionnaires and tracking their behavior, as with Pear Therapeutic’s products) and information about (non-)adherence is just one piece of information analyzed together with other data, when an algorithm produces so-called ‘individualized variability signatures’,¹⁰⁹ these should be meaningful in a specific context that makes sense for a particular patient and they need to be discussed with the patient’s physician.¹¹⁰ Otherwise, it becomes

107 Laura Lovett, *Pear Therapeutics Inks Deal With Digital Pill Company etectRx*, <https://www.mobihealthnews.com/news/pear-therapeutics-inks-deal-digital-pill-company-etectrx> (accessed Jan. 24, 2022).

108 Jessica Morley & Luciano Floridi, *Enabling Digital Health Companionship Is Better Than Empowerment*, 1 LANCET DIGIT HEALTH e155–6 (2019).

109 Ilan, *supra* note 16.

110 GERALD YOUNG, UNIFYING CAUSALITY AND PSYCHOLOGY: BEING, BRAIN, AND BEHAVIOR (2016).

very easy to penalize those who decide not to follow the recommendations of the algorithm. Arguably the sensor seems to have a different logic. The following section will further explore this point.

IV. THE INTERESTS OF A COMPANY MAKING AN INGESTIBLE EVENT MARKER

Proteus, the first company to apply for authorization of an ingestible sensor, has presumably deliberately proceeded with a ‘five-tier’ strategy: *first*, demonstrate that the system is safe and effective for confirming that a pill has been taken; *second*, show that the system is safe and effective for monitoring the ingestion of a pill; *third*, show that the system is safe and effective for confirming that a pill has been taken and for monitoring of the taking of the pill when the pill *also* contains a drug itself acknowledged as safe and effective; *fourth*, demonstrate that the system *improves* actual intake of a prescribed drug; and *fifth*, show that the system improves intake of *any* drug, and thus that FDA approval should be granted for the combination of *any* approved drug and the Proteus IEM. Interestingly, *this strategy need never involve clinical trials by Proteus to demonstrate improved clinical outcome for patients, something particularly relevant in the light of the very high percentage of patients who are not clinically responsive to many drugs.* Schork, for example, reports that the top 10 bestselling drugs in the USA have a clinical response rate of ‘only’ between one in four and one in 25 patients, with the response rate for aripiprazole being one in five.¹¹¹

As far as improvement of actual pill intake is concerned, for Otsuka and, perhaps to a greater extent, for Proteus, once Abilify MyCite was in large-scale use, comparison between the actual pill intake rates for aripiprazole recorded over years for patients taking the conventional pill and those recorded for Abilify MyCite would show whether actual pill intake was indeed improved by using Abilify MyCite. The use of such ‘real world data’ might serve to achieve or accelerate FDA approval. For Otsuka, approval of Abilify MyCite for improving ‘adherence’ would, in and of itself, represent a major victory, since Abilify MyCite could then ‘legally be advertised to’ interested parties, for example physicians, insurers, and national health services, *for that purpose.* For Proteus (or any other company making ingestible sensors), it would facilitate obtaining approval for the IEM itself for improving pill intake and thus make approval for that purpose, for use in combination with ‘any’ other drug, much cheaper and more straightforward.¹¹² This would extend the range of pharma companies that Proteus might have targeted as potential licensees and would have opened the possibility for Proteus itself to produce new IEM-plus-drug combination pills for drugs that are currently generic, and thereby reap profits beyond those attainable by licensing its system to pharma

111 Schork, *supra* note 3.

112 Proteus had tried showing that its IEM improves actual intake rates for *any* drug, and this is highlighted by the fact that in April 2018, Proteus had announced that it had formulated 15 digital medicines (which it called ‘DigiMeds’) for cardiovascular and metabolic conditions. In infectious disease, the company had seven digital medicines that are being used in clinical studies to treat patients with TB, hepatitis C and HIV and the company was developing a portfolio of digital medicines for cancer patients. See Proteus Digital Health, *Proteus Digital Health announces digital medicines pipeline development and expansion into oncology*, <https://www.businesswire.com/news/home/20180425005798/en/Proteus-Digital-Health%2%AE-A-nnounces-Digital-Medicines-Pipeline-Development-and-Expansion-into-Oncology> (accessed Jan. 25, 2022).

companies. Indeed, Proteus has tried to do this.¹¹³ Now that Otsuka has acquired Proteus' intellectual property rights, pairing with generics or other companies is open to Otsuka rather than to Proteus.

The IEM aims at ensuring compliance rather than adherence in the sense of the Shared Decision-Making model that we mentioned in Sections II and III. Let us take a look at how the IEM is described in Proteus' US Patent No. 7978064 (meanwhile acquired by Otsuka).¹¹⁴ The IEM design should make it possible to eliminate or reduce 'gaming' by the patient, for example where the patient seeks to avoid taking the medication or even wishes to sell the medication to others, something of particular concern with opioids or other street-sellable drugs. Such 'gaming' might occur when the patient simply puts the digital pill in a beaker of acid so as to simulate intake, or where the patient separates the IEM from the pill, swallows the IEM, and sells on the remains of the pill.

Turning to the next component, the torso-worn patch, as explained above, is much more than a transceiver sending a yes/no signal to the patient's mobile phone to confirm whether or not the digital pill has been swallowed. The patch itself is designed to collect and transmit to the mobile phone more patient-related data than simply relates to pill ingestion. The patch collects physiological and behavioral metrics including heart rate, activity, body angle, and time-stamped user-logged events generated when a user marks an event by swallowing an IEM or by manually pressing an event marker button on the patch. The patch stores and wirelessly sends the IEM data to a general computing device.¹¹⁵ Otsuka admits that the system could be used to 'locate' (ie track) the patient.¹¹⁶

In short, for providers of systems to remotely monitor medication intake, the goal is quite simply to make a profit. The profit can come either from providing the monitoring system, from offering a digital pill using the monitoring system, or from using the data they accrue from the use of their monitoring system (either directly to increase use of their system or indirectly by selling or licensing data or algorithms derived from the data, not necessarily for healthcare purposes or indeed for the benefit of the patients from whom the data derive). In all cases, they need to maximize the use of their monitoring system, and this means demonstrating that their system is superior to other competing systems, either in terms of increasing adherence by willing patients or in terms of identifying non-compliant patients or patient types, ie by game-proofing their systems.

Thus, for the provider of a pill intake monitoring system, the initial goal can generally be expected to be to grant drug-specific exclusive licenses to pharmaceutical manufacturers and/or to grant institution-wide licenses to healthcare systems. A longer-term goal could be to become suppliers of generic pharmaceuticals themselves with

113 Rebecca Robbins, *A 'Digital Pill' for Cancer Patients Is Rolled Out for the First Time, in Hopes of Improving Outcomes*, STAT NEWS, Jan. 17, 2019, <https://www.statnews.com/2019/01/17/a-digital-pill-for-cancer-patients-is-rolled-out-for-the-first-time-in-hopes-of-improving-outcomes/> (accessed Jan. 25, 2022).

114 Mark Zdeblick, Timothy Robertson, Aleksandr Pikelný & Hooman Hafezi, *Communication System With Partial Power Source*, U.S. Patent No. 7,978,064 (filed Sep. 21, 2009).

115 FDA, *supra* note 40.

116 Lisa Henderson, *Specialty Product Launch Insights*, 38 PHARM. EXE., Sept. 1, 2018, <http://www.pharmexe.com/specialty-product-launch-insights/> (accessed Jan. 25, 2022).

retention of exclusivity for these drugs to themselves. As noted earlier, Proteus seemed to have been on this track.

Finally, system providers will seek to make whatever financial benefit they can from the secondary uses of the patient data they have amassed and of any (behavioral or other) predictive analytics they develop. The phenotypic patient databases they develop might conceivably be thought to have values similar to those of the phenotype-/genotype databases being amassed by direct-to-consumer genomics companies.¹¹⁷

V. THE DRUG MANUFACTURER

For the drug manufacturer, the goal is simple—to allow sales volume and profit to be maximized. This simply requires (at least partial) exclusivity for the combination of the monitoring system and the company's drug (as opposed to competing equivalent or generic drugs). Reaching this goal also requires the healthcare system or the insurer to be convinced of the improved pill intake being real. Duration of marketing exclusivity is paramount—the longer the better. However, it is in the interests of the drug maker that the system they license exclusively is more attractive to healthcare systems and insurers than any other competing system.

At this stage, we must turn the spotlight on the 'elephant in the room', namely generic substitution, a system whereby pharmacists, presented with a prescription for a drug specifying a brand name (eg Abilify) rather than the drug's open name (eg aripiprazole), are permitted or even required by law or contract to supply the patient with a cheaper generic equivalent for the drug, and where the physician herself may be required to prescribe the drug under its open name. The financial consequences are immense, as can be seen for the case of aripiprazole, where the US price for a 30-day supply of Abilify MyCite is estimated at \$1640, of the conventional branded version Abilify at \$940, and of the generic at about \$30. For the pharmaceutical manufacturer, generic substitution of a digital pill by a 'digital generic' gives rise to a reduction in company profit.¹¹⁸ The manufacturers therefore have a clear interest in a medication intake monitoring system that is proof from such generic substitution.

In cases where the pill required for intake monitoring is itself a 'combination product', the conventional pill is 'not' a generic equivalent that can be substituted by the pharmacist when prescribed by a physician. Accordingly, as long as the combination product (eg drug plus IEM) is covered by a patent and/or by data exclusivity, the combination product strategy of the Proteus system provides the pharmaceutical manufacturer with protection against competition. As noted above (Section I), Otsuka acquired Proteus' intellectual property rights. This means that they can essentially evergreen their patents by means of making incremental improvements to the sensor and apply for new patents covering the new combination product (reference blinded for review). What is more, as one of us has argued elsewhere (reference blinded for review) these patents are for systems that facilitate 'data generation', in the sense that the data collected can be amassed in datasets, which are well kept trade secrets, and which can be used to train an algorithm that makes recommendations to patients. As

117 Heidi Howard et al., *The Convergence of Direct-to-Consumer Genetic Testing Companies and Biobanking Activities: The Example of 23andme*, in KNOWING NEW BIOTECHNOLOGIES. SOCIAL ASPECTS OF TECHNOLOGICAL CONVERGENCE 59–74 (Matthias Wienroth & Eugénia Rodrigues ed., 2015).

118 Beriain & Gonzalez, *supra* note 31.

mentioned earlier, digital pills of the future may look very different: they will likely be AI-based and seek to tailor therapeutic regimens to specific patients, for example by means of a user-friendly app that the patient can download to a cell phone to receive a therapeutic regimen.¹¹⁹ What is more, using the data accrued by using the invention (the digital pill), the pharmaceutical company may not only reinforce its position in a specific market but also leverage its position to neighboring markets, for example using algorithms for early identification of non-compliant individuals that can also be useful for early-stage drug trials.

VI. HEALTH SERVICES AND INSURANCE PROVIDERS

Health services and insurance providers are important stakeholders. As regards insurers, interestingly, one commentator discussing the Proteus system argues that:

[I]n...the insurance [context] we could regard [tracking medication intake] as merely another aspect of the transactional relationship between...insurer and insured.... [E]ach party has goals. Both parties accede to the other's demands to some degree, although the power imbalance means that the insured [does] so to a much greater extent. But...the insured...can make a free choice that the benefits of insurance...are worth the 'cost' of being tracked and providing data. This cost may not be terribly high, either, given that the patient arguably loses little by being tracked. If he or she gains lower premiums or can demonstrate desired adherence...they may in fact benefit in return for agreeing to be tracked.... [T]he insured party is at a severe disadvantage in relation to the insurer when he or she is seeking insurance, so it is perhaps unrealistic to conceptualise their exchange as entirely freely transactional. But if we consider the points at which the law tends to consider consent to transactions vitiated, such pressure falls well short of the requirements for duress in contract, and is closer really to the kinds of commercial pressures accepted as the norm in contract negotiations.¹²⁰

However, in addition to the fact that the patient may lose a lot, rather than little, by being tracked, we would question whether such pressures on individuals are acceptable at all in the context of healthcare. Of course, insurers and healthcare providers will naturally seek to optimize their use of funds. For example, in 2012, the Centers for Medicare and Medicaid Services in the USA added new criteria for deciding how many stars (one to five) to award to Medicare Advantage plans. Quality measures were added concerning 'adherence to oral hypoglycemic drugs, some antihypertensive medications, and lipid-lowering agents.... For health plans to achieve 5 stars, more than 75% of their beneficiaries will need to obtain at least 80% of the medication prescribed to them'.¹²¹ The calculations are currently done on the basis of prescription refill records,¹²² but of course it is conceivable to use more efficient systems when available for this purpose. Currently, the Centers for Medicare and Medicaid Services mention, *inter alia*, measures for 'adherence' to: statin therapy, angiotensin-converting

119 Ilan, *supra* note 16.

120 See Goold, *supra* note 31, at 16. Goold applies the same argumentation to medication intake tracking of employees by employers. We will not go into this aspect here.

121 John F. Steiner, *Rethinking adherence*, 157 ANN. INTERN. MED. 580 (2012).

122 Centers for Medicare & Medicaid Services, *Quality Measures* (2019), <https://www.cms.gov/medicare/quality-initiatives-patient-assessment-instruments/qualitymeasures/> (accessed Feb. 3, 2022).

enzyme inhibitors, angiotensin receptor blockers, oral diabetes agents, antipsychotic medications, mood stabilizers, and antiplatelet therapy.¹²³

For healthcare services or insurers, the ‘benefit’ of the medication intake tracking systems is assurance that pills are taken and that, if not, the healthcare service could change its way of ensuring uptake and the insurer could withdraw insurance cover. If the healthcare system itself undertakes clinical trials, then further benefits to the system might accrue (see [Section VIII](#)). The ‘downsides’ are: first, the higher cost; second, the problem of patient cheating; and third, and perhaps most importantly, the erosion of trust. Cheating will depend on the extent to which the system adopted is game-proof. As to erosion of trust, in choosing a digital pill, the healthcare system or insurer risks losing patient and societal trust unless the digital pill is purely a ‘voluntary’ option for the patient.

A further advantage of digital pills may be their effect in ‘nudging’ patients towards better compliance—however, this applies only if the system is voluntary, it requires a nudge not a leash. Nonetheless, some physicians go as far as to argue that ‘to have the largest public health effects, measures of medication adherence [sic] should be included in the electronic health record... [which] will allow for sharing among health care professionals and insurers’.¹²⁴ Similarly, as pointed out in a recent review article:

Mobile health data are likely to be more useful if combined with EHR data for patient or clinician use. Recent technology is making this possible. In the Apple ecosystem, the Apple Health app can, for example, pull in data from a wrist sensor as well as EHR data from the patient’s health care institution or institutions. The Android CommonHealth app aims to duplicate this functionality for Android smartphones. Once sensor and EHR data are on a smartphone, they can be made available to other apps on the phone, combined with data reported by patients, or sent up to a cloud to be computed into more aggregated digital biomarkers or used with machine learning to drive decision support.¹²⁵

To many readers, it may seem that US-style private insurance paid healthcare and the directly or indirectly nationally funded healthcare systems in Europe pose entirely different problems in the adoption of digital pills. We would beg to differ even though there are still substantial differences between healthcare insurance practices in the USA and Europe. For example, in Europe, health insurance systems remain more government-driven and less dominated by private insurers than in the USA. However, cost containment is also high on the agenda of government-driven systems. Also, in Europe, there are already some interventions for which reimbursement is stopped if patient compliance is insufficient, for example for the use of Continuous Positive Airway Pressure masks for obstructive sleep apnea, and for some glycaemia lowering drugs. It is thus certainly not inconceivable that similar concerns about motivations could also increasingly affect European insurance systems and that digital pills might accelerate this.

123 *Id.*

124 Zachary A. Marcum et al., *Medication Nonadherence—A Diagnosable and Treatable Medical Condition*, 309 *JAMA* 2105, 2105–6 (2013).

125 Ida Sim, *Mobile Devices and Health*, 381 *NEJM* 956, 960 (2019).

VII. THE PHYSICIAN

The benefit to the physician is confirmation that the patient is taking her medication so reducing any perceived obligation to check up on her. However, the fact that there is an opportunity to know the status of medication intake potentially raises an obligation on the physician to react if the patient is not following her prescription. This raises the problem of data overload, and the question of when and how physicians should act. As one of the readers commenting on a *Washington Post* article on the Proteus system asks: ‘What is the doctor going to do? Drive over and give the pill?’, or, as observed by another commentator: ‘I am a physician and I for one don’t want the responsibility to be a “pill nanny”’.¹²⁶

A too low alert threshold will result in alert fatigue and a too high threshold questions the very concept of tracking intake. The question arises as to whether the physician would be liable if the system was to fail or if the physician would fail to react to an alert.

Many of the concerns mentioned in the previous section for the patient ‘also’ arise for the physician, albeit in different form. The patient’s medical record is also accessible by the physician, and with data on medication intake and other data going beyond the patient and her physician, concerns must also arise concerning their confidentiality and the possibility of the data being used for purposes not agreed to or not known to the physician. In this case however, the physician faces the added risk that her performance is ‘also’ being monitored and that she may in some way be punished, for example in a liability action or by her direct or indirect fee payer (eg an insurer, a healthcare system, a hospital, or joint practice). Moreover, the very availability of medication intake monitoring systems may result in the physician’s autonomy being curtailed—for patients of this category or with that illness, digital systems must be used and, perhaps, patient visits reduced. In such cases, the quality of the physician–patient relationship may be reduced, job satisfaction might decrease and moral distress may increase. Furthermore, since physicians’ prescribing practices are regularly monitored by the pharmaceutical companies, the appearance of a digital alternative to a much cheaper generic may result in undesirable pressures being put on the physician.

Nonetheless, if the use of digital pills is voluntary, the physician may see a benefit insofar as her patients are ‘nudged’ towards better adherence, and so potentially better health. However, as stated before, in the optimal setting of Shared Decision-Making, these tracking systems are clearly disproportionate, as simpler techniques such as alerting and educational apps could be used to achieve these goals.

VIII. CLINICAL TRIAL INVESTIGATORS

Where a digital pill is taken as part of a clinical trial, the benefit to ‘the trial investigator’ is reassurance that the drug has actually been taken by the patient in the trial and the trial results may be perceived as more trustworthy. One drawback, that the pill is more expensive, is in most trials negligible in the context of overall trial costs. For trial investigators, just as for physicians and insurers as discussed above, the question of patient cheating arises. Can the patient persuade the tracking system that she has taken her pill when she has not?

126 Rowland, *supra* note 58.

However, using a tracking device for medication in a clinical trial challenges the interpretation of the study results and requires sufficient consideration of an ‘intention to treat’ versus an ‘as treated’ approach, transportability, and generalizability issues, as well as the question of how attrition due to side effects is handled. These are already serious concerns regarding the validity and representativeness of randomized controlled trials,¹²⁷ which will only be exacerbated by the use of pill intake tracking systems.

We can identify four distinct categories of clinical trials and the benefits and concerns are not the same in each case: first, trials of new drugs, done by or for the pharmaceutical company wishing to bring the drug to the market; second, trials to demonstrate the efficacy of a known drug for a new indication; third, trials to demonstrate whether a digital version of a generic drug is superior to the conventional version; fourth, trials by or for healthcare systems, for example to determine whether a digital pill offers significant benefits over a conventional pill, or to determine which of several alternative drugs offers the ‘best’ results.

In the case of a new drug, the digital pill offers the trial operator the possibility to select ‘compliant’ test subjects based on characteristics identified by the system providers, to limit the results used for regulatory clearance to those from subjects with a high likelihood of actually taking the drug. Companies might do this to speed up completion of trials (as less drop out occurs) and to improve the chances of a positive outcome (as more compliant patients often have better outcomes).

However, a strategy involving excluding non-compliant patients from trials seriously hampers the generalizability of findings to the real world and results in an inflated expectation of results in the real world.¹²⁸ Furthermore, it seriously reduces the occurrence of ‘informative drop out’. In an RCT without selection of compliant participants, patients might stop taking the drug when they develop an unpleasant side effect, whereas this is less likely to happen if the trial cohort consists of patients selected for their known compliance. Even when there is no pre-trial patient selection, a comparable problem could arise if only patients actually taking the drug are analyzed. There is potential information in the fact that patients stop taking a medication, perhaps unpleasant side effects, or perhaps lack of effect. As a consequence, the results of the trial will not be representative of the effects in the real world.

For drugs that are, or are shortly to become, generic, where the IEM and the drug already have separate regulatory approval, the drug manufacturer needs minimal regulatory approval for a digital pill and, with an exclusive license for the combination from the system provider, needs only post-approval trials demonstrating an improvement in actual pill intake that outweighs the extra price over the conventional generic for the insurer or healthcare system to make the digital pill commercially viable.

In clinical trials run by healthcare systems, the use of digital pills theoretically offers the trial operator the possibility to reduce trial size by patient selection, and the results could theoretically enable the healthcare system to optimize cost/benefit by selection between competing drugs or between digital and conventional versions of

127 See, e.g., Peter M. Rothwell, *Factors That Can Affect the External Validity of Randomized Controlled Trials*, 1 PLOS CLINICAL TRIALS e9 (2006).

128 We should point out that, in RCTs of antipsychotics, this is common practice.

pills containing the same drug. However, the reliability of the conclusions will again be highly dependent on the methodology used to analyze the data. As for the previous cases, there might be problems of generalizability, and therefore, not all patients will necessarily benefit. In reality, some patients might even be harmed if the healthcare system's resulting drug of choice is less appropriate for the individual patient.

Lastly, we would point out that the patient in trials involving only digital pills might feel her freedom of action is constrained by the accompanying day-by-day surveillance.

IX. DATA USERS

As explained by Sim in a recent review article on mobile devices and health, a mobile phone has various 'sensor' capacities:

It has a nine-axis inertial motion sensor that tracks motion and position in three-dimensional space. A three-axis accelerometer measures acceleration in the x, y, and z axes; a three-axis gyroscope senses rotation around each axis; and a three-axis magnetometer compensates for magnetic drift to maintain position accuracy.¹²⁹

As Google, Amazon, Facebook, Cambridge Analytica, etc. well know, the more data you have on people, the more closely you can target advertisements onto them and the higher your earnings/value. Our digital footprint, the result of our interaction with mobile phones and computers (eg keyboard strokes), allegedly opens a window into behavior and mental health.¹³⁰

Proteus promoted their system as collecting and aggregating behavioral, physiological, and therapeutic data, and competed in the market for such metrics. Goold places much emphasis on the perceived adequacy of data protection laws such as the EU *General Data Protection Regulation* (GDPR)¹³¹ in preventing 'leakage' of health information from within the physician-patient relationship.¹³² She states that the GDPR 'would restrict doctors receiving the information from sharing it without patient consent'.¹³³ However, she seems to overlook the fact that the data are received by the system provider 'directly and automatically' from the patient's phone. In systems such as this, the physician is 'not' the gatekeeper.

The data the system providers collect, even if 'anonymized' or aggregated, could enhance the services these companies provide or might be sold on. For instance, data brokers accumulate and link data about the same individuals from many different sources, including administrative records from multiple government agencies and commercial data from other sources. The profiles compiled are sold to other businesses, including banks and retail, and linked to yet more data sources. Privacy of personal data seems barely possible as group profiling affects even those who have not given consent to the use of their data in the first place. For example, Huckvale et al. have examined the

129 Sim, *supra* note 128, at 956.

130 Thomas R. Insel, *Digital Phenotyping. Technology for a New Science of Behavior*, 318 JAMA, 1215 (2017).

131 EU, *Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)*, L119, 59 OFFICIAL JOURNAL OF THE EUROPEAN UNION 4 May 2016, 1, 1–88.

132 Goold, *supra* note 31.

133 *Id.* at 9.

handling of data by 36 smartphone apps that assisted people with either depression or smoking cessation, to find that 33 apps shared their data with third parties, despite the fact that just 25 of those apps had a privacy policy at all and out of those, only 23 stated that data would be shared with third parties.¹³⁴ Notably, the data collected went almost exclusively to Facebook or Google.

Sherman explains:

some large data brokers like Acxiom advertise literally thousands or tens of thousands of individual data points on a given person. At that breadth (from sexual orientation and income level to shopping receipts and physical movements across a mall, city, or country), the collective profile on each individual looks unique. At that depth (from internet searches to 24/7 smartphone GPS logs to drug prescription doses), many single data points within each person's profile can also be unique. It's all too easy for those organizations—and anyone who buys, licenses, or steals the data—to link all that back to specific people.¹³⁵

Montgomery notes the possible privacy problems of digital pills but suggests that these can be sufficiently reduced either by the imposition of use constraints by the lawmaker to limit the ability of the parties involved to collect, store, and use the data generated by digital pill systems, or by improving the notice and consent requirements placed on a physician when prescribing a digital pill.¹³⁶ Montgomery considers that use constraints are less desirable as they may hinder the rollout of the benefits of digital pills and so should only be imposed after a thorough cost–benefit analysis. The notice and consent procedure she advocates in preference to use constraints seems to closely match the system discussed in Otsuka's Terms and Conditions of Use and Patient Privacy Notice.¹³⁷

According to Beriain and González, '[i]t is good to highlight that patients can decide who has access to their data at any moment among other authorized parties, such as Otsuka and its vendors, their selected healthcare providers, their family and friends, their pharmacy, or their health plan'.¹³⁸ However, Otsuka's Patient Privacy Notice for the Abilify MyCite System shows that this is not the case:

Your Patient Personal Information may be shared with a trusted vendor to create de-identified data. To create de-identified data, the vendor will remove certain pieces of identifying information. Deidentified data will not contain any information that could be used to contact or readily identify you, but the data may not be completely anonymous. The vendor may combine your Patient Personal Information with personal information

134 Kit Huckvale et al., *Unaddressed Privacy Risks in Accredited Health and Wellness Apps: A Cross-sectional Systematic Assessment*, 13 BMC MED. 214 (2015).

135 Justin Sherman, *Big Data May Not Know Your Name. But It Knows Everything Else*, WIRE, Dec. 19, 2021, <https://www.wired.com/story/big-data-may-not-know-your-name-but-it-knows-everything-else/> (accessed Jan. 25, 2022).

136 Montgomery, *supra* note 61.

137 Otsuka, *Terms & Conditions of Use and Patient Privacy Notice* (2018), <https://www.otsuka-us.com/sites/g/files/qhldwo4361/files/media/static/Abilify-Mycite-Patient-Terms-of-Use-and-Privacy-Notice.pdf> (accessed Feb. 5, 2022); Otsuka, *Terms & Conditions of Use and Patient Privacy Notice* (2020), <https://www.otsuka-us.com/sites/g/files/qhldwo4361/files/media/static/Abilify-Mycite-Patient-Consent.pdf> (accessed Feb. 5, 2022).

138 Beriain & Gonzalez, *supra* note 31, at 2. See also Rosenbaum, *supra* note 59 for a similar view.

collected from other System users to create de-identified, aggregated data. We hold all rights, title, and interest in and to de-identified data. We reserve the right to use, share, and commercialize de-identified data (regardless of whether it has been aggregated) for any purpose, in our sole judgment.¹³⁹

Of course, digital pills are not the only means for amassing health data that raise surveillance concerns.¹⁴⁰ To give another example, the Apple Watch, a wearable approved as a medical device via the ‘de novo’ procedure by the FDA in 2018, is sold directly to consumers. It can collect a variety of biometric data and it has a built-in electrocardiograph.¹⁴¹ Moreover, fitness trackers such as Fitbit, web searches, social media posts, and shopping histories, can also reveal information about an individual’s health.¹⁴² These collections of health data ‘outside’ the health system provide a detailed picture of users’ health, termed ‘shadow health records’.¹⁴³ In fact, the rapidly evolving field of ‘digital phenotyping’ presents a hybrid between a science of behavior/psychiatry and data analytics, seeking to infer behavior and mental states from data collected from various devices.¹⁴⁴ So what is specific to digital pills? Adherence is one metric of behavior which might point to relapse and possible hospitalization. Data with regard to adherence can be used for the purposes of making better risk predictions by means of identifying populations at risk of relapse and possible hospitalization. Given that lack of adherence to treatment is one of the indicators of relapse or heightened risk for people with schizophrenia to have worse long-term outcomes,¹⁴⁵ data about adherence to medication can be important when building algorithms predicting risk of clinical deterioration. However, once the act of not taking your pills ‘becomes a proxy for’ relapse, adherence falls back to compliance as expressed in the idea that a patient did not follow doctor’s orders. Hence the crucial differences between ‘adherence’ and ‘compliance’, as discussed in detail earlier in this article (Section III), are lost.

X. SOCIETY AT LARGE

For society at large, medication intake monitoring systems may offer certain advantages, for example in terms of: reduced risk of spreading infection, of increased drug resistance by microbes, and of drug abuse (by reducing possibilities to resell drugs); better health prospects for friends and family (provided, of course, as should be emphasized again, that taking the drugs in question actually improves health); and more rapid appearance of new drugs on the market by speeding up clinical trials, although,

139 Otsuka (2018), *supra* note 140, at 13.

140 We thank one of the anonymous reviewers for highlighting this.

141 Apple, *Apple Announces Effortless Solution Bringing Health Records to iPhone* (2018), <https://www.apple.com/newsroom/2018/01/apple-announces-effortless-solution-bringing-health-records-to-iphone/> (accessed April 27, 2022).

142 ADAM TANNER, *OUR BODIES, OUR DATA: HOW COMPANIES MAKE BILLIONS SELLING OUR MEDICAL RECORDS* (2017).

143 W. Nicholson Price et al., *Shadow Health Records Meet New Data Privacy Laws*, 363 *SCIENCE* 448 (2019).

144 Valeria de Angel et al., *Digital Health Tools for the Passive Monitoring of Depression: A Systematic Review of Methods*, 5 *NPJ DIGIT. MED.* 3 (2022).

145 Higashi et al., *supra* note 92. Other indicators include the effects of concurrent conditions, and social and financial impoverishment.

as explained earlier, clinical trials involving digital pills raise various additional issues regarding reliability of the trial results.

However, these monitoring systems are associated with several disadvantages, first of all of course increased tax and insurance costs, given the enormous price difference between the conventional and digital pills. As noted by one of the commentators to a *Washington Post* article on the Proteus system: ‘this isn’t an advance in care; this is an exercise in how to leverage tech to jack the price of an old product into the stratosphere’.¹⁴⁶

Another disadvantage is the awareness that at some future time, when we ourselves become patients for whom digital pills are prescribed or required, our autonomy may be curtailed, and our data may be used for purposes that we are not in agreement with.

XI. SOME RECOMMENDATIONS

Existing studies provide thin evidence and insight into the challenges of digital pills. Evidence is scant, based on small samples, and there is a lack of studies comparing the accuracy of digital pills with other traditional methods (such as pill counts or self-reporting), which is surprising given the digital surveillance and high privacy risks.¹⁴⁷ We would argue that for ‘digital pill’ or other medication intake-improving systems, constraints beyond the normal ones of safety and efficacy applied by regulatory agencies, such as the FDA, are required. The controls that are required seem to fall into four major categories: patients, disease conditions, data collection and use, and market exclusivity.

In the complex ecosystem of digital health, stakeholders are driven by diverging incentives. Patients, regulators, pharmaceutical and other commercial companies, healthcare providers, researchers, policy makers, and investors have different targets. While the FDA and EMA have narrow safety and efficacy concerns, crucial to understanding the problems raised by digital pills and similar monitoring systems is to realize that they stem from the desire of commercial players to use legal strategies to obtain and extend monopolies covering medical treatments. However, we should not forget that the proper purpose of exclusivity-granting systems in relation to drugs (eg the patent system) is to encourage the arrival of new drugs and new uses of them rather than to ‘extend’ the high-profit making period granted in relation to old drugs and their uses, i.e. ‘not’ to facilitate so-called evergreening.¹⁴⁸ In this way, society at large may benefit as much as possible and as soon as possible as is commensurate with allowing the pharmaceutical innovators to recoup their expenses, to make a reasonable profit, and then to be simply one among the many suppliers who are free to compete on a level playing field with generic producers of the drug.

Besides the inflation of drug prices, questions arise as to limitation of patient autonomy and uses of patient data in ways that seem to be incompatible with the Shared Decision-Making model. Our analysis of various patents covering these systems for remote monitoring of medication intake has revealed that the logic of the system is one of obtaining patient compliance (rather than adherence) and avoiding risks of

146 Rowland, *supra* note 58.

147 Martani et al., *supra* note 13.

148 See, e.g., Cosgrove et al., *supra* note 7.

‘gaming the system’. In order to safeguard autonomy, it is essential that these systems function as complements or companions rather than substitutes for a good therapeutic relationship, given the complex reasons behind non-intake of medication.

More research on this topic is definitely needed, but we would recommend that the rollout of digital pills ought to be ‘restricted’ to situations involving ‘both’:

- (a) drugs that are subject to a criminal market (drugs and substances, which pose a significant risk of Substance Abuse Disorder, eg opioids), or drugs the failure to take which will within a short time be life-threatening or disabling; *and*
- (b) incompetent patients, *or* competent patients who have genuinely consented and who have a non-digital alternative on offer at no higher cost in money, effort, or reputation (ie risk of stigmatization).

At the same time, we would recommend that, where digital pills or similar technologies ‘are’ permitted outside the aforementioned situations: (i) (maintenance of) regular checkups on the patients be required and (ii) that all system providers should be required to disclose exactly which data are collected, how its security or confidentiality is ensured, and to whom it is disclosed (both with and without anonymization, aggregation, and transformation) and under what conditions of cost, confidentiality, or use. Such disclosures should be publicly accessible with minimum effort and in terms understandable to persons with the minimum locally required level of education and should include a reasoned explanation for the collection of each type of data (eg location, internet use, etc.). Furthermore, data collected by the system providers should not be allowed to be sold to third parties, given that other companies can also monetize them for numerous purposes as well as linking them to other patient data which they are able to purchase already. Where drug manufacturers produce products used with such systems, they should moreover be required to make available to the local regulatory agency details of all information they receive from the systems suppliers, together with reasoned explanations for the necessity of each type of data received.

Obviously, a key aspect of Digital Health is the use of patients’ personal data, which poses a number of questions from a legal perspective. Both FDA controls and CE marking in Europe seem inadequate. In Europe, there has been a turn to regulate these harms with legislative instruments such as the *General Data Protection Regulation* (2016/679). In fact, it has been recently argued by Ienca & Malgieri¹⁴⁹ that the safeguards of the *General Data Protection Regulation* in the EU may be applicable in the case of ‘digital mind technology’ and ‘mental data’ defined as any data that can be organized and processed to infer the mental states of a person (including cognitive, affective, and connate aspects). If we take the example of an algorithm that would purport to predict relapse of psychiatric patients on the basis of data on adherence, it seems that data derived from sensors embedded into digital pills may fall under the category of ‘mental data’, since they would be used to infer mental states (eg deterioration of a mental

149 Marcello Ienca & Gianclaudio Malgieri, *Mental Data Protection and the GDPR*, 9 J. LAW BIOSCI. January–June (2022), lsac006.

health condition). Ienca and Malgieri argue that ‘mental data’ are personal data,¹⁵⁰ and they may even qualify as sensitive data due to the ‘characteristics’ of mental data processing for purposes such as profiling, scoring, and the systematic monitoring of individuals, especially in the case of vulnerable individuals. Therefore, these authors call for a ‘Mental Data Protection Impact Assessment’ requiring data controllers to describe their processing of data, to assess the risks involved, and to propose ways to mitigate harms to fundamental rights and freedoms.

Health Technology Assessment (HTA) bodies can also play an important role since they look into the broader effects on society of novel technologies by means of summarizing information about medical, economic, social, and ethical issues related to the use of a health technology. HTA bodies are conceived as a way to identify intended effects of technologies as well as unintended social, economic, and environmental effects.¹⁵¹ In the USA, there is no national HTA program to evaluate health technologies as the system relies on privately funded HTA bodies. Member States of the European Union have national HTA bodies, which provide recommendations on medicines and other health technologies financed or reimbursed by the healthcare system in a Member State.¹⁵² This system is currently changing with the entry into force of the new EU *Regulation on Health Technology Assessment 2021/2282* in January 2022¹⁵³ (the Regulation will be applied in January 2025). The Regulation focuses on clinical aspects of HTA such as clinical effectiveness and clinical safety of a new health technology as compared with existing technologies. Importantly, in the future, Member States will be able to also include an assessment of economic aspects of a health technology. External experts (including clinicians) and patients, will be able to provide input during the preparation of Joint Clinical Assessment reports (prepared by groups of national representatives), and Member States will be required to give due consideration to the Joint Clinical Assessment reports in their national HTA processes.

Moreover, in April 2021, the European Commission released its proposed *Regulation Laying Down Harmonized Rules on Artificial Intelligence* that is currently a hot topic of debate. The new AI Regulation (AIA) would complement the Medical Device Regulation, requiring that an AI-based medical device meets additional requirements so that it is ‘secure and trustworthy’. The proposed AI Regulation may be relevant to future ‘generations’ of digital pills, which may combine a personalized AI system with a branded or generic drug which has an embedded sensor tracking the ingestion of a pill.

150 Hence, the purposes of data processing should be specified, explicit, and legitimate (Article 5(1)(b) GDPR). The authors note that if the data controller processes mental data, for example for health self-monitoring purposes, and then uses those data for commercial purposes, they commit a violation of the purpose limitation principle.

151 Robert M. Margolis & David H. Guston, *The Origins, Accomplishments, and Demise of the Office of Technology Assessment*, in *SCIENCE AND TECHNOLOGY ADVICE FOR CONGRESS* 53–76 (M. Granger Morgan & Jon M. Peha ed., 2003); European Network for Health Technology Assessment, *Assessment FAQ. What is Health Technology Assessment (HTA)* (2018), <https://www.eunetha.eu/services/submission-guidelines/> (accessed June 1, 2022).

152 EMA, *Health technology assessment bodies*, <https://www.ema.europa.eu/en/partners-networks/health-technology-assessment-bodies> (accessed June 1, 2022).

153 Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (Text with EEA relevance) *PE/80/2021/INIT OJ L 458, 22.12.2021*.

We noted that these sensors collect a variety of physiological data (heartbeat, movement, etc.) and can be combined with data from other data sources. It is argued that this is aimed at the forgetful patient and that the AI analytics will provide useful information about their health status more generally. However, when analyzing the relevant patents, one can see that the companies in question describe their technologies as something that seeks to ensure that patients do not ‘game the system’ and that they take their pills.

If such technologies aim to identify people who do not take their medication (and disadvantage or punish them), they should fall under the remit of the proposed AI Regulation as a ‘high risk AI system’ and consequently additional safeguards would be required, so that the technologies may fulfill their promise of being an ‘empowering’ personalized tool. The European Commission states that high-risk AI systems should only be placed on the EU market ‘if they comply with certain mandatory requirements’ that ensure they do not pose unacceptable risks to important public interests (such as fundamental rights). They must put a quality management system in place (proposed Article 17 AIA), draw up the technical documentation (proposed Article 18 AIA), ensure that their systems undergo the relevant conformity assessment procedure (proposed Article 19 AIA), keep the automatically generated logs (proposed Article 20 AIA), take appropriate corrective measures when they consider or have reason to consider that a high-risk AI system which they have placed on the market or put into service is not in conformity with the regulation (proposed Article 21 AIA), comply with a duty of information if the system presents a risk within the meaning of the proposed Article 65(1) of the proposed AIA (proposed Article 22 AIA), and, upon request by a national competent authority, provide that authority with all the information and documentation necessary to demonstrate the conformity (proposed Article 23 AIA).¹⁵⁴ A similar notable development is the Council of Europe’s Ad hoc Committee on Artificial Intelligence (CAHAI) recommendation for a legally binding treaty on AI that would protect democracy, human rights, and the rule of law, and which includes the right to choose interaction with a human in addition to or instead of an AI system.¹⁵⁵

XII. CONCLUDING REMARKS

Whereas some medications do have life-saving properties, the systems we discuss here could be applied to many conditions which are ‘not’ life-threatening to patients or other community members. In these latter cases, tracking actual intake can be considered disproportionate, as there is no overriding benefit. While an individual might be prepared to spend her own money on a not particularly beneficial technology, it is not in the general interest for social systems (tax or insurance) to do so. Thus,

154 See Gloria González Fuster & Michalina A.N. Peeters, *Person Identification, Human Rights and Ethical Principles: Rethinking Biometrics in the Era of Artificial Intelligence. Study Prepared at the Request of the Panel for the Future of Science and Technology (STOA)* (2021), [https://www.europarl.europa.eu/stoa/en/documents/EPRS_STU\(2021\)697191](https://www.europarl.europa.eu/stoa/en/documents/EPRS_STU(2021)697191) (accessed Jan. 25, 2022).

155 Ad Hoc Committee on Artificial Intelligence (CAHAI). LEGAL FRAMEWORKS GROUP (CAHAI-LFG) OUTCOME FROM SUB-WORKING GROUP 2 PREPARED BY CAHAI-LFG SUB-WORKING GROUP 2 (31 MARCH 2021), <https://rm.coe.int/cahai-lfg-2021-03-outcome-swg2-2783-5500-1603-v-1/1680a1f7c0> (accessed Jun. 15, 2022).

while in principle we accept that there are circumstances where the limitation of patient autonomy and privacy by such systems *can* be justified, our analysis suggests that such systems pose a significant risk of unacceptable damage to patient autonomy and Shared Decision-Making in (psychiatric) medicine.

Incorrect medication intake arises from a highly complex interplay between ‘personal’ factors, ‘illness-related’ factors, and ‘treatment-related’ factors. It should be seriously questioned whether remote intake monitoring systems are the best way forward to address the potential problems caused by incorrect medication taking. If a simple alerting device could achieve comparable results in forgetful patients ‘consenting’ to take the medication, remote intake monitoring would be disproportionate. As discussed earlier, there is no evidence that digital pills or similar technologies improve medication intake. In patients ‘not consenting’ to take the medication, and where a simple alerting system would thus be insufficient, these systems arguably act as a straightjacket to enforce ‘compliance’. Although the terms ‘(non-)compliance’ and ‘(non-) adherence’ are frequently used as synonyms, they are not. Indeed, the differences between them are highly relevant to an exploration of the implications of digital pills for patient autonomy. While the concept of compliance disregards the patient’s perceptions on medication taking, the concept of adherence implies that the appropriate treatment is decided after discussion between the physician and the patient, who share responsibility for a treatment plan. We have argued that the concept of adherence entails that the patient has agreed and consented to take the medication because she understands that this is important in order to achieve health-related goals that she values. In such circumstances, if the patient fails to actually take the drug, this can only represent ‘non-adherence’ where the patient forgot or where external factors beyond the patient’s control prevented the drug from being taken. A simple alerting system, for example a mobile phone app, would seem sufficient to prevent the problem arising from forgetfulness. In these situations, tracking the actual drug intake is unnecessary, disproportionate, intrusive, and overly complex.

While the rhetoric employed in support of the adoption of digital pills is that adherence will be improved, the underlying drive for their adoption seems instead to be that compliance can be achieved. This issue is even more concerning in view of the multiple forms and levels of bias and discrimination in psychiatry, as discussed in our overview of many relevant recent studies.

In general, we find that in relation to this technology, the public policies regarding the granting of patents and of marketing approval overly favor the interests of commercial actors and seriously risk disregarding the interests of patients. We therefore proposed that the roll-out of digital pills ought to be restricted to specific situations and that digital pills that use AI for ‘personalization’ may need to be classified as high risk systems that require additional safeguards such as those mentioned in the proposed AI Regulation in the EU.

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