DIGITAL HEALTH STRATEGIES - AROUND THE PILL

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Abstract:

The goal of a global strategy on digital health is to encourage wellness and healthy living for all people, in every place, and at all stages of life. National or regional digital health projects need to be supported by a strong strategy that combines organizational, human, economic, and technological assets in order to realize their true potential. Digital Pills are an advanced drug-device technology that enables the association of conventional drugs with a monitoring system that automatically records patient physiological data as well as information regarding medication adherence. Digital adherence technology may offer promising patient-focused approaches to adherence monitoring. A variant of the subsequent generations of antipsychotic aripiprazole that was implanted with a sensor (Abilify MyCite) received FDA approval in November 2017. The study focuses on the digital health strategies and impacts around the pill and offers a thorough analysis of it.

Introduction [1]

The broad scope of digital health encompasses fields like wearable technology, telehealth and telemedicine, customized medicine, and mobile health (mHealth).

Digital technology continues to be driving a transformation in health care, from machine learning and artificial intelligence (AI) to mobile medical applications and software that assist the clinical decisions clinicians undertake every day. The use of digital health technologies has the potential to significantly improve individual patient care by enhancing the accurate diagnosis and treatment of disease.

For healthcare and associated purposes, digital health technologies employ computer platforms, networking, software, and sensors. These technologies have a wide range of applications, including those for medical devices and applications for general well-being. They consist of innovations designed to be used as medical products, as auxiliary diagnostics, or in conjunction with other medical goods (devices, medications, and biologics). They could also be utilized to research or create medicines [2].

Digital health technologies benefits:[3][4]

Through data access, digital tools are offering healthcare professionals a more comprehensive picture of patient health and also allowing people greater control over their own health. Real potential to increase productivity and improve medical outcomes is presented by digital health.

These technologies provide new opportunities for assisting prevention, and early identification of life-threatening illnesses, as well as management of chronic ailments outside of conventional medical settings [49]. They can also enable customers to make better choices regarding their own health. Digital health technologies are being used by professionals and other stakeholders to:

- Reducing inefficiencies
- enhancing accessibility
- lowering costs
- raising quality
- Personalizing medication for patient is a goal.

Digital health technology can help patients and customers to manage and keep track of their actions linked to their health and wellness.

Mobile devices, social media platforms, and internet apps are altering the way we interact, but they are also enabling us to track our health and well-being in novel ways and expanding our access to information. In order to enhance medical treatment and medical outcomes, these developments are bringing together people, information, technology, and connection [5].

Emphasis on digital health

These days, a lot of medical equipment can link and communicate with other equipment or systems. Digital features are being added to devices that have previously received FDA approval, authorization, or clearance. These features are being investigated in new gadget kinds [6][7].

Patients, healthcare professionals, researchers, conventional medical device sector companies, and companies that are new to the FDA regulatory standards, including mobile application developers, are just a few of the stakeholders participating in digital health activities.

These developments and consumer technology, networking, and medical devices excite the FDA's Centre for Devices and Radiological Health (CDRH). The FDA has been striving to clarify the following issues in the realm of digital health by using realistic strategies that analyse risks and benefits:[8][9]

- Health IT
- Medical Device Data Systems
- Medical Device Interoperability
- Telemedicine
- Wireless Medical Devices
- Software as a Medical Device (SaMD)
- Artificial Intelligence and Machine Learning (AI/ML) in Software as a Medical Device
- Cybersecurity
- Device Software Functions, including Mobile Medical Applications

To encourage the uptake and expansion of electronic health and innovation, there are three main goals to be achieved:[10]

1. **Putting the most recent data, investigation, and evidence into practice:** This entails supporting the development of digital tools that aid in informed decision-making as well as requirements for accessibility and data sharing.

2. **Increasing knowledge through professional communities in science:**

The WHO brings together leading expert perspectives on issues of clinical and health-related importance without being constrained by the necessity for formal meetings or printed peer-reviewed journals [11].

3. **systematically evaluating and correlating innovation supply with national needs:** Too frequently in global health, goods are created with the assumption that "if you develop it, they will utilize it." This strategy has consistently failed. In order to find, encourage, co-develop, and scale inventions that are based on national requirements, WHO adopts a proactive, systematic approach [12].

STRATEGIC OBJECTIVES FOR DIGITAL HEALTH:[13][14]

The four strategic goals are meant to offer direction and coordination for the worldwide transformation of digital health and to build synergies between programs and stakeholders to enhance health outcomes and reduce related risks across all levels.

1. Promote international cooperation and knowledge transfer in digital health

Implementation of digital technologies are mostly related to health Sustainable Development Goals, and universal health coverage. The strategy aims to align nations and stakeholders to act collectively upon worldwide opportunities for better health and work toward this goal while addressing challenges, recognizing and disclosing risks, as well as concentrating on the threats associated with this use [48]. Regardless of the situation, it promotes action on shared opportunities and problems that are pertinent to all stakeholders and countries. Thus, maximize the influence of new and current partnerships and collaborations within the larger digital health ecosystem. Healthcare technology design and execution are common across disciplines, as are investments in them;

Therefore, this strategic objective seeks to strengthen existing relationships and forge new ones with nations, other stakeholders, and other United Nations system organizations.

Examine and spread awareness of the most recent, useful, and inventive health innovations. New and cutting-edge medical services and solutions are being developed thanks to innovative technologies in health care. This sub-objective makes it possible to analyze the effectiveness and quality of innovative health technologies in order to facilitate their prompt adoption and promotion. To assure the investment, conservation, quality, and security of both digital health goods and cutting-edge health technology that may be directly sold to consumers as well as utilized in healthcare. So, norms, standards, laws, and regulations are required. Global direction, coordination,

and application for their acceptance and incorporation into current services and systems at the federal level of capabilities [47] .

2. **Ensure that national digital health plans are implemented more quickly:[15]**

The second strategic objective aims to encourage and assist each nation in taking ownership of adapting, and strengthening its digital health strategy in a manner that best fits its vision, national context, health condition and trends, available resources, and fundamental values. This strategic goal promotes the creation of a national strategy on the digital health sector through an all-inclusive multistakeholder approach, taking into account the following essential elements and factors working together within communities of practice:

(1) leadership and governance; (2) investment and operations; (3) scaling-up services and applications; (4) integration and sustainability, while respecting: (5) standards and interoperability; (6) a flexible digital infrastructure; (7) a workforce with a flexible approach to healthcare; and (8) legislation, ethics policies, and compliance; and a people-centered strategy: (9). To guarantee that the requirements and expectations with the available resources are satisfied, these all ought to be created while the essential alignment of national stakeholders is ensured.[48]

In order to coordinate assets and make investments in order to guarantee the sustainability and expansion of digital health, the strategic objective intends to create cross-sector collaborations at the national level. The goal also aims to improve international digital health initiatives by collaborating with current digital health partnerships. Member States' adoption of digital health innovations would be accelerated by the creation of national partnerships for their sustainability [47]. However, this strategic objective is to create institutional and human capacity enabling secure and appropriate usage and scale of each country's plan from concept to execution of digital health by boosting the commitment and methodical participation of each stakeholder in all countries. The purpose underlies the promotion of creative integration of digital technology into health systems [16].

Finding strategies to increase capacity and develop a digitally adept health staff are important goals in the effort to enhance health systems by adopting digital technology. The needs will differ from nation to nation, but they frequently involve the creation of a competent workforce in the fields of technology and health, as well as leadership and governance [46].

3. **Strength global, regional, and national governance for digital health:[17]**

By developing strong and sustainable governance mechanisms and increasing the capacity for the advancement of digital health on a global and national scale, this strategy aims to improve the management of digital health at both the national and international levels. The purpose of governing for the field of digital health is to improve the capacities and competencies required for countries to advance, invent, and build up digital health innovations [50].

The strategic goal encourages the upholding of high standards for data privacy, security, interoperability, and safety both inside and beyond the health industry. Defining principles and coming to cross-sectoral and international agreements for data sharing, the reliability and precision of health data, and the order of importance of investment plans and policies are all actions that should be taken to enhance governance [45]. It should also provide ethical guidelines for the use of health data in big data and artificial intelligence applications. Additionally, it seeks to advance research on the use of electronic health records in the healthcare industry as well as the measurement and tracking of it.

The research program should take into account the requirement to enhance and share data and knowledge on the utilization of digital health services at all levels. To support its safe application, to create and encourage accountability, and to justifiably explain the financial investment, research on and assessment of the outcomes and impacts of digital health are crucial. The need to encourage the creation and testing of technological advances, processes, and infrastructures that get around barriers to applying digital health to health goals should also be on the table. The enhancement and sharing of methodologies and data analytics, as well as enhancing the capacity of research teams, are all strongly related to this objective [18].

4. **Encourage the use of digital health to support people-centered healthcare systems:[19]**

The advancement of health information literacy, gender equality, women's empowerment, and inclusive strategies to the use and administration of digital health technology are all goals of this strategic aim. Through the implementation and utilization of technological advances in digital health enhancing and expanding the provision of medical services, the strategic aim places individuals at the center of digital health. The individual plays a crucial role in the provision of trustworthy, patient-centred care [43]. Along with patients, families, and communities, this focus includes health professionals who must be ready to adopt or use technology for digital health in their jobs. Workforce assessment is a part of planning for capacity-building and involves individuals in technology-related fields as well as healthcare providers. Being inherently multidisciplinary and interdisciplinary, building capacity entails fostering abilities, attitudes, and skills that, based on a digital health application and its context, may range from the fields of computer science, business strategy, finance, and leadership, to health sciences and care delivery. The effect of integrating digital technologies and managing them

on the health labour market should be taken into account while evaluating the workforce. To achieve this goal, nations would need to switch from their existing disease-focused systems to an interconnected one that puts the patient first. It's important to address attitudes about, usage of, and public knowledge of digital health [44]. Actions that might be taken include raising the general population's level of digital health literacy, including patients, families, and communities, and teaching patients about their own health improved response to Civil society as well as other industries and actors will need to be included in order to strengthen digitally enabled disease systems' support for social and economic determinants of health. A further measure to take into consideration is raising knowledge of and access to evidence-based self-management tools [20].

The digital medical system's technology:[21]

The use of a digital medicine system, which combines a drug with an ingestible sensor that is capable of sending a signal when the drug-device combination is exposed to gastric acid in the stomach, is the most recent innovation. This type of technology enables factual-time knowledge of medication intake. It is thought that doing this will enhance drug compliance, which should lead to better health outcomes and cost savings [22]. Digital medicine systems offer the ability to improve patient care in a number of ways, including by enhancing prescription adherence, monitoring drug usage in real-time, and reducing the risk of misuse and overdose [23][24]. The DSM is a mobile device that belongs to the patient that wirelessly links to their medical records and automatically uploads their medicine [25]. An approach is to employ wireless technology with electrochemical sensing methods [26].

The components of the digital medication are a wearable sensor patch, a mobile computing device, and an ingestible sensor of 1 (mm)2 size that is embedded in an oral solid preparation like a tablet. Metals that are ingestible, including copper and magnesium, are coated on the sensor. The sensor produces a message that is sensed by the patch after being consumed and being triggered by stomach fluid. In comparison to their respective permitted quantities for human intake of 0.3% (7.7 mg) and 0.003% (9.8 mg), respectively, the quantity of copper and magnesium that may be absorbed by the gut from the digestible sensor is very little.
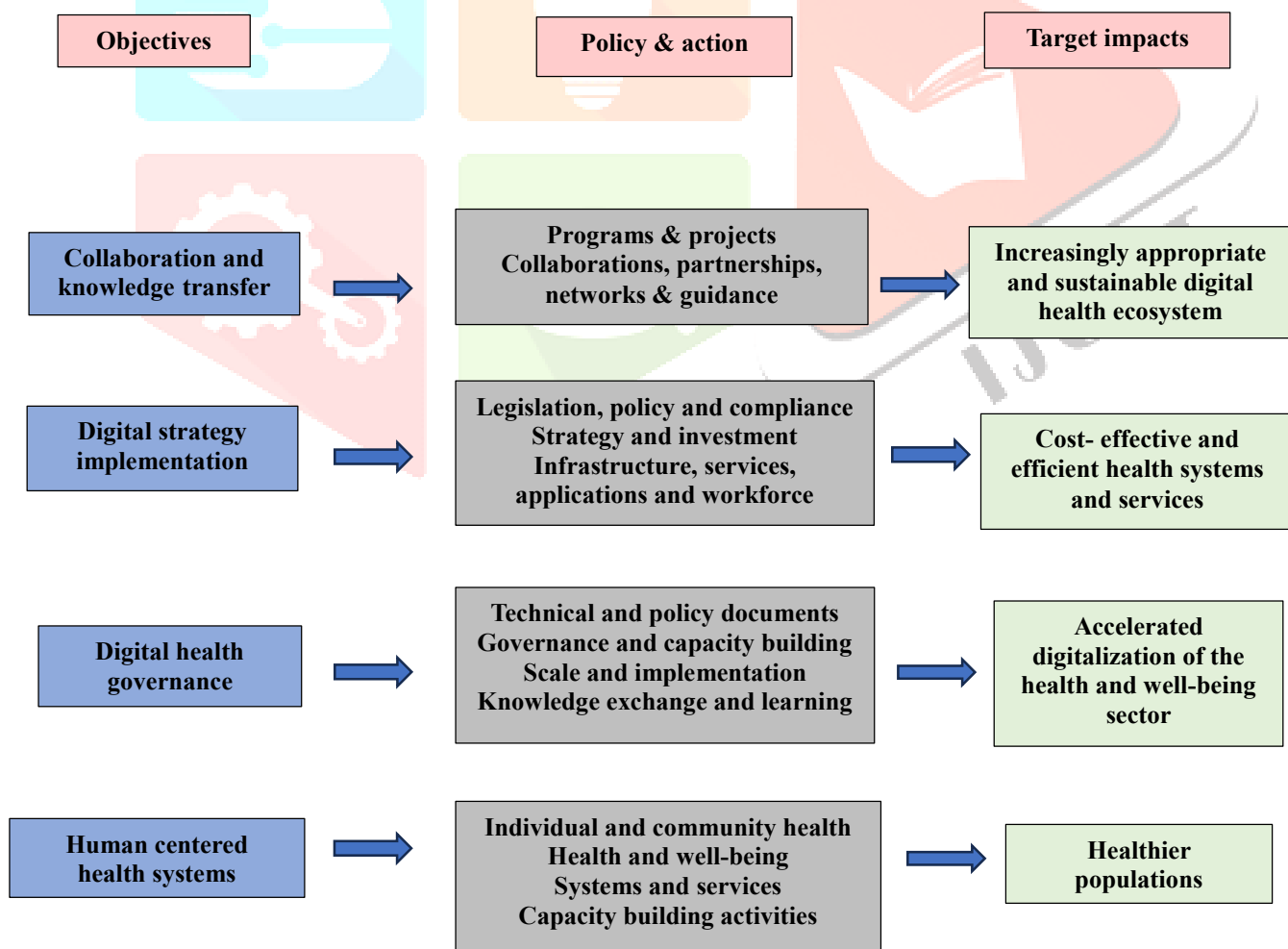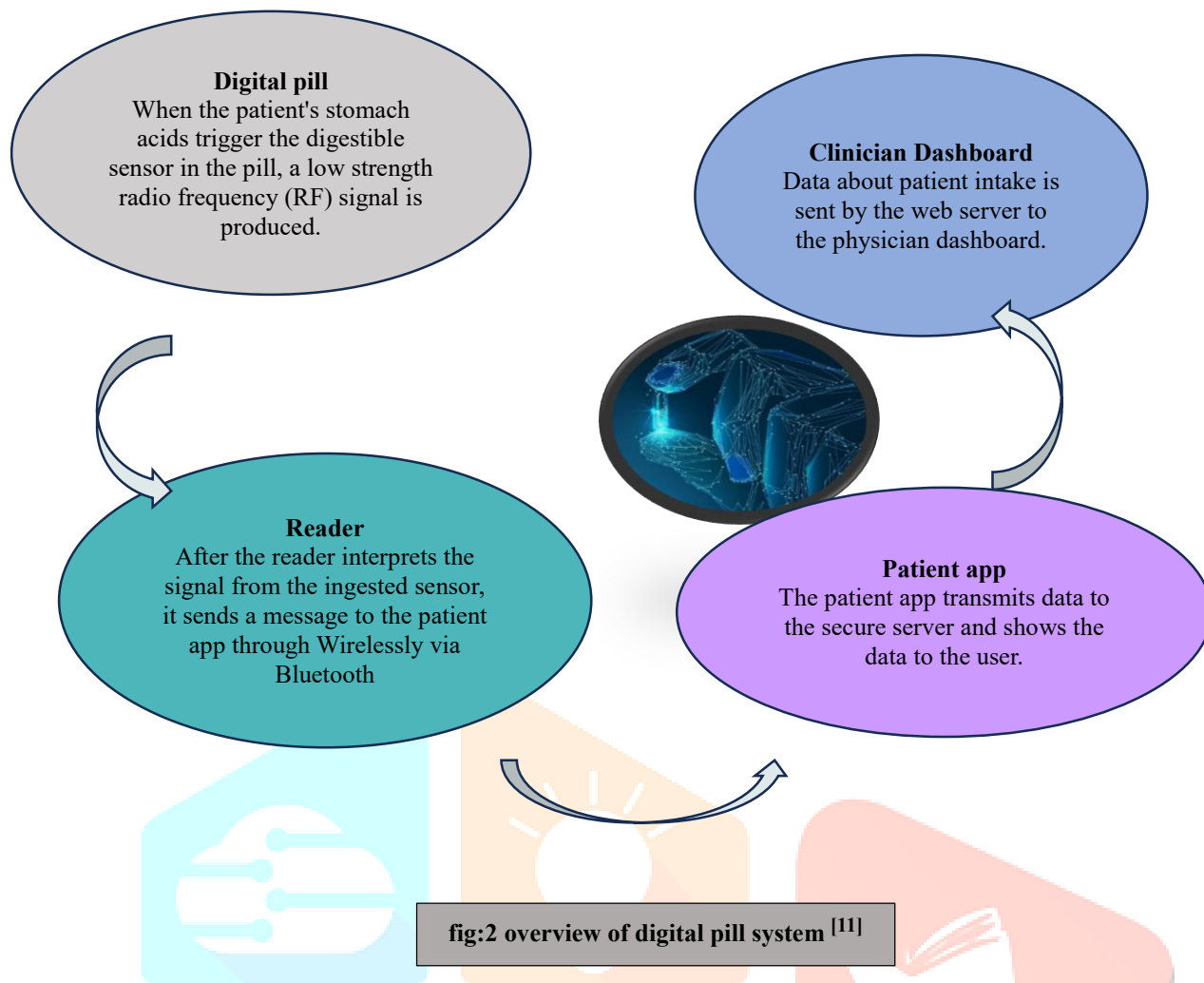

fig:1 summary of implementation and impacts of digital health **strategies** [14]

The body-worn wearable sensor patch is around 10 cm in length and detects and records the time and date of consumption of medicine. The glue is held in place by a foam surface, which also offers the electronics of the gadget a waterproof casing. The upper body (torso) is where it should be applied, and it may be worn for the majority of activities, including exercise and bathing. The glue needs to be changed every week since water and a lot of activity might cause the patch to come off [27]. For patients with severe mental illness, a unique Digital Medicine System (DMS) has been created to accurately monitor and record consumption of the atypical antipsychotic aripiprazole [28]. DMS serves as a smart medicine reminder; smart medication reminder systems are meant to assist elderly persons with satisfying themselves by taking their meds at the precise time and in the proper dosage, but they are not limited to doing so [29]. System collects medication information from the user, including the length of the prescription, the names of the medications, the time they should be taken, and the recommended dosage for each. After all of this information has been successfully entered, the system will notify the user by smartphone notification and a physical reminder, at the appropriate time, which medication has to be taken [29].

Digital pills:

Smart Notifications Digital pills are made out of a gelatin capsule that has the required drug combined inside of a digital radiofrequency emitter. The chloride ion gradient in the stomach activates the radiofrequency emitter when it is swallowed, causing it to broadcast a distinct signal. The Health Information Technology for Economic and Clinical Health (HITECH) and the Health Insurance Portability and Accountability Act (HIPAA)--compliant cloud-based server receive information about the identity of the taken medication and the time of ingestion from a hip-worn receiver that detects this signal. Digital tablets cannot be activated outside of the body since they are keyed up by the particular chloride ion gradient in the stomach. This technology can record the signal because each digital pill produces a distinct frequency. Multiple simultaneous ingestion events can be recorded by the system. The Food and Drug Administration in the USA assesses both pharmaceuticals and medical devices [30]. A smart insulin pen, a smart pill, and a smart inhaler are among recent drug-device combinations that the Food and Drug Administration (FDA) has authorized [31]. The use of digital pills, which are novel, easy to use, and passively evaluate adherence, reduces the need for a person to interact with technology while transmitting adherence data [32]. initially approved digital medication to get the market is an antipsychotic, despite the fact that the DSM technology has primarily been tested on people with physical disorders. 'Abilify MyCite' was the first medication to be authorized by the Food and Drug Administration (FDA) on November 13, 2017 [33]. Utilizing an electronic intake monitoring system [34–36]. These antipsychotic drugs have a sensor that can be ingested and connects to an internet site, a smartphone app, and a wearable patch. A collection of several technologies, including trackers, sensors, patches, applications, programming, smartphones, and the internet, make up Abilify MyCite. It makes use of science and technology studies (STS) and new materialism to argue that ingestible sensors and other new pharmaceuticals are creating a data-driven subjectivity, which has the potential to revolutionize mental health treatment [37]. This term refers to the inextricability of data, its processing and production, and the establishment of subjectivity. Atypical antipsychotic drug aripiprazole has a 30% endogenous dopamine agonist activity. Aripiprazole exhibits antagonist capabilities at 5-HT2A receptors and furthermore displays a partial agonist activity on 5-HT1A receptors [38]. The current Proteus Discover® Label states that the ingestible sensors are recognized with 98% sensitivity and with 100% accuracy of identification [39]. The ingestible sensor and wearable sensor patch were created and marketed by Proteus Digital Health, Inc., which received FDA clearance in 2012. They created the digital drug Abilify® (aripiprazole) through their collaboration with Otsuka Pharmaceutical [40]. This is the very first time the FDA has approved an application for a novel drug for a digital medication for revision. After reaching the stomach, the sensor in the digital medication Abilify® (aripiprazole) delivers a signal to the wireless sensor patch [41]. Patients receive this information via a cell phone or other Bluetooth-enabled device, only with the approval of their medical professionals and/or caretakers [27]. Schizophrenia, bipolar disorder, and depression are all conditions that are treated with Abilify MyCite [42]. It combines aripiprazole with a digital sensor that, once implanted in the stomach, connects with a patch worn by the patient and records the time, date, and dose of the drug automatically [42].

Digital pill
When the patient's stomach acids trigger the digestible sensor in the pill, a low strength radio frequency (RF) signal is produced.

Clinician Dashboard
Data about patient intake is sent by the web server to the physician dashboard.

Reader
After the reader interprets the signal from the ingested sensor, it sends a message to the patient app through Wirelessly via Bluetooth

Patient app
The patient app transmits data to the secure server and shows the data to the user.

fig:2 overview of digital pill system [11]

Conclusion:

DMS lays the groundwork for future studies on the digital health strategies, advantages, and drawbacks of expanding the use of digital pills and traditional pharmaceuticals. According to FDA HF guidelines, DMS is the first integrated digital health product created in the field of psychiatry. It offers significant advantages for addressing adherence concerns that are not possible with conventional therapeutic methods. A sustainable healthcare system might be achieved through the use of digital medicine. They clearly mark the beginning of a new era in healthcare.

REFERENCES

[1] Hagan MJ, Adashi EY. Implied Yet Unproven: The Digital Pill–Present and Future. Rhode Island Medical Journal. 2020 Oct 1;103(8):23-4

[2] Plowman RS, Peters-Strickland T, Savage GM. Digital medicines: clinical review on the safety of tablets with sensors. Expert opinion on drug safety. 2018 Sep 2;17(9):849-52

[3] Martani A, Geneviève LD, Poppe C, Casonato C, Wangmo T. Digital pills: a scoping review of the empirical literature and analysis of the ethical aspects. BMC medical ethics. 2020 Dec;21:1-3.

[4] de Miguel Beriain I, Morla González M. 'Digital pills' for mental diseases: an ethical and social analysis of the issues behind the concept. Journal of Law and the Biosciences. 2020 Jan;7(1):lsaa04

[5] Papola D, Gastaldon C, Ostuzzi G. Can a digital medicine system improve adherence to antipsychotic treatment?. Epidemiology and psychiatric sciences. 2018 Jun;27(3):227-9

[6] Richey AG, Kovacs I, Browne S. Use of an Ingestible, Sensor-Based Digital Adherence System to Strengthen the Therapeutic Relationship in Serious Mental Illness. JMIR Mental Health. 2022 Dec 2;9(12):e39047.

[7] Blazer DG, Domnitz S, Liverman CT, for Adults AH, National Academies of Sciences, Engineering, and Medicine. Hearing health care services: improving access and quality. Hearing Health Care for Adults: Priorities for Improving Access and Affordability. 2016 Sep 6.

[8] Ilancheran M. Use Of Wearable And Sensor Applications In Clinical Trials Is Booming.

[9] Litvinova O, Klager E, Tzvetkov NT, Kimberger O, Kletecka-Pulker M, Willschke H, Atanasov AG. Digital pills with ingestible sensors: Patent landscape analysis. Pharmaceuticals. 2022 Aug 19;15(8):1025.

[10] Rahman T. Should trackable pill technologies be used to facilitate adherence among patients without insight?. AMA Journal of Ethics. 2019 Apr 1;21(4):332-6.

[11] Chai PR, Goodman GR, Bronzi O, Gonzales G, Baez A, Bustamante MJ, Najarro J, Mohamed Y, Sullivan MC, Mayer KH, Boyer EW. Real-world user experiences with a digital pill system to measure PrEP adherence: perspectives from MSM with substance use. AIDS and Behavior. 2022 Jul;26(7):2459-68.

[12] Goodman GR, Kikut A, Bustamante MJ, Mendez L, Mohamed Y, Shachar C, Cohen IG, Gerke S, Boyer EW, Rosen RK, Mayer KH. "I'd feel like someone was watchin'me… watching for a good reason": perceptions of data privacy, access, and sharing in the context of real-time PrEP adherence monitoring among HIV-negative MSM with substance use. AIDS and Behavior. 2022 Sep;26(9):2981-93.

[13] Roemmich K, Andalibi N. Data subjects' conceptualizations of and attitudes toward automatic emotion recognition-enabled wellbeing interventions on social media. Proceedings of the ACM on Human-Computer Interaction. 2021 Oct 18;5(CSCW2):1-34.

[14] https://www.who.int/health-topics/digital-health#tab=tab_1

[15] Siddesh Shewalkar K, Sakshi Kothawade M and Rupali Patil A, "Digital Pills: Impact of Rising Technology" in Archives of Medicine, 2021, 13 (6:26), 1-6.

[16] Akkermans J, de Lange AH, van der Heijden BI, Kooij DT, Jansen PG, Dikkers JS. What about time? Examining chronological and subjective age and their relation to work motivation. Career Development International. 2016 Aug 8;21(4):419-39.

[17] Egilman AC, Ross JS. Digital medicine systems: an evergreening strategy or an advance in medication management?. BMJ Evidence-Based Medicine. 2019 Dec 1;24(6):203-4.

[18] Vallejos X, Wu C. Digital medicine: innovative drug-device combination as new measure of medication adherence. Journal of Pharmacy Technology. 2017 Aug;33(4):137-9.

[19] Mc Caffrey C, Twomey K, Ogurtsov VI. Development of a wireless swallowable capsule with potentiostatic electrochemical sensor for gastrointestinal track investigation. Sensors and Actuators B: Chemical. 2015 Oct 31;218:8-15.

[20] Minaam DS, Abd-ELfattah M. Smart drugs: Improving healthcare using smart pill box for medicine reminder and monitoring system. Future Computing and Informatics Journal. 2018 Dec 1;3(2):443-56.

[21] Batra S, Baker RA, Wang T, Forma F, DiBiasi F, Peters-Strickland T. Digital health technology for use in patients with serious mental illness: a systematic review of the literature. Medical Devices: Evidence and Research. 2017 Oct 4:237-51.

[22] Kopelowicz A, Baker RA, Zhao C, Brewer C, Lawson E, Peters-Strickland T. A multicenter, open-label, pilot study evaluating the functionality of an integrated call center for a digital medicine system to optimize monitoring of adherence to oral aripiprazole in adult patients with serious mental illness. Neuropsychiatric Disease and Treatment. 2017 Oct 19:2641-51.

[23] Jongsma KR, Bredenoord AL, Lucivero F. Digital Medicine: An Opportunity to Revisit the Role of Bioethicists. The American Journal of Bioethics: AJOB. 2018 Sep 1;18(9):69-70.

[24] Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC, Coker-Schwimmer EJ, Rosen DL, Sista P, Lohr KN. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. Annals of internal medicine. 2012 Dec 4;157(11):785-95.

[25] Banchs JE, Scher DL. Emerging role of digital technology and remote monitoring in the care of cardiac patients. Medical Clinics. 2015 Jul 1;99(4):877-96.

[26] El Hadidi S, Rosano G. Evidence beyond the digital medication pill. European Heart Journal-Cardiovascular Pharmacotherapy. 2020 Mar 1;6(2):72-4.

[27] Minaam DS, Abd-ELfattah M. Smart drugs: Improving healthcare using smart pill box for medicine reminder and monitoring system. Future Computing and Informatics Journal. 2018 Dec 1;3(2):443-56.

[28] Peters-Strickland T, Pestreich L, Hatch A, Rohatagi S, Baker RA, Docherty JP, Markovtsova L, Raja P, Weiden PJ, Walling DP. Usability of a novel digital medicine system in adults with schizophrenia treated with sensor-embedded tablets of aripiprazole. Neuropsychiatric Disease and Treatment. 2016 Oct 11:2587-94.

[29] Frigerio M. Getting approval for new therapeutic medical devices versus drugs: are the differences justified?. European Respiratory Review. 2016 Sep 1;25(141):223-6.

[30] Zijp TR, Mol PG, Touw DJ, van Boven JF. Smart medication adherence monitoring in clinical drug trials: a prerequisite for personalised medicine?. EClinicalMedicine. 2019 Oct 1;15:3-4.

[31] Chai PR, Carreiro S, Innes BJ, Rosen RK, O'Cleirigh C, Mayer KH, Boyer EW. Digital pills to measure opioid ingestion patterns in emergency department patients with acute fracture pain: a pilot study. Journal of medical Internet research. 2017 Jan 13;19(1):e19.

[32] Dotolo D, Petros R, Berridge C. A hard pill to swallow: ethical problems of digital medication. Social work. 2018 Oct 1;63(4):370-2.

[33] Papola D, Gastaldon C, Ostuzzi G. Can a digital medicine system improve adherence to antipsychotic treatment?. Epidemiology and psychiatric sciences. 2018 Jun;27(3):227-9.

[34] Hunt S, Hellwig JP. FDA Approves First Digital Medicine System. Nursing for Women's Health. 2018 Feb 1;22(1):12.

[35] Flore J. Ingestible sensors, data, and pharmaceuticals: Subjectivity in the era of digital mental health. New Media & Society. 2021 Jul;23(7):2034-51.

[36] Fischer B, Davids E, Gastpar M. Aripiprazol-Pharmakologie eines neuen atypischen Antipsychotikums. Fortschritte der Neurologie· Psychiatrie. 2004 Sep;72(09):497-502.

[37] Van Biesen W, Decruyenaere J, Sideri K, Cockbain J, Sterckx S. Remote digital monitoring of medication intake: methodological, medical, ethical and legal reflections. Acta Clinica Belgica. 2021 May 4;76(3):209-16.

[38] Swartz AK. Smart pills for psychosis: the tricky ethical challenges of digital medicine for serious mental illness. The American Journal of Bioethics. 2018 Sep 2;18(9):65-7.

[39] Mulder T, Jagesar RR, Klingenberg AM, Bonnici JP, Kas MJ. New European privacy regulation: Assessing the impact for digital medicine innovations. European Psychiatry. 2018 Oct;54:57-8.

[40] Hird N, Ghosh S, Kitano H. Digital health revolution: perfect storm or perfect opportunity for pharmaceutical R&D?. Drug discovery today. 2016 Jun 1;21(6):900-11.

[41] Klugman CM, Dunn LB, Schwartz J, Cohen IG. The ethics of smart pills and self-acting devices: autonomy, truth-telling, and trust at the dawn of digital medicine. The American journal of bioethics. 2018 Sep 2;18(9):38-47.

[42] Young MA, Dimartino L. Trackable pill digital technology in PRM & pain: Hype or hope?. Annals of Physical and Rehabilitation Medicine. 2018 Jul 1;61:e115.

[43] Focsa S. What can be done for access and reimbursement processes to reward innovation in digital "beyond the pill" solutions?. Value in Health. 2017 Oct 1;20(9):A708.

[44] Focsa S. What can be done for access and reimbursement processes to reward innovation in digital "beyond the pill" solutions?. Value in Health. 2017 Oct 1;20(9):A708.

[45] Vayena E, Ienca M. Digital medicine and ethics: rooting for evidence. The American Journal of Bioethics. 2018 Sep 2;18(9):49-51.

[46] Mulder T, Jagesar RR, Klingenberg AM, Bonnici JP, Kas MJ. New European privacy regulation: Assessing the impact for digital medicine innovations. European Psychiatry. 2018 Oct;54:57-8.

[47] Cosgrove L, Cristea IA, Shaughnessy AF, Mintzes B, Naudet F. Digital aripiprazole or digital evergreening? A systematic review of the evidence and its dissemination in the scientific literature and in the media. BMJ evidence-based medicine. 2019 Dec 1;24(6):231-8.

[48] Akkermans J, de Lange AH, van der Heijden BIJM, Kooij DTAM, Jansen PGW, Dikkers JSE (2016) "What about time? Examining chronological and subjective age and their relation to work motivation". Career Dev Int 21: 419-439.

[49] Egilman AC, Ross JS. Digital medicine systems: an evergreening strategy or an advance in medication management?. BMJ Evidence-Based Medicine. 2019 Dec 1;24(6):203-4.

[50] Vallejos X, Wu C. Digital medicine: innovative drug-device combination as new measure of medication adherence. Journal of Pharmacy Technology. 2017 Aug;33(4):137-9.