GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(REVIEW ARTICLE)

Check for updates

The future of medication adherence: Exploring the potential of digital pills

Prajwal Sunil Kole, S P Hiremath *, M Mahesh Yadav, Gouri Santosh Koshti and Anisha Anandu Shetiya

Department of Pharmaceutics, KLE College of Pharmacy, Vidyanagar, Hubballi, Karnataka, 580031. India.

GSC Advanced Research and Reviews, 2025, 23(02), 080-093

Publication history: Received on 30 March 2025; revised on 14 May 2025; accepted on 17 May 2025

Article DOI: https://doi.org/10.30574/gscarr.2025.23.2.0134

Abstract

The modern healthcare landscape is increasingly influenced by digital health technologies, particularly with the introduction of sensor-integrated digital pills. These digital pills (DP) merge traditional treatment approaches with systems that monitor both medication adherence and patient's physiological conditions. Medication non-adherence is a major global challenge, particularly in the management of chronic illnesses. Effectively addressing this issue requires a blend of educational initiatives, behavioural approaches, and cooperation between patients and healthcare providers. This review explores a variety of digital tools designed to enhance medication management and adherence, including mobile applications, online platforms, smart pills, dispensers, packaging, and ingestible sensor. Additionally, medication adherence is often overstated in clinical trials, potentially leading to reduced statistical power and misleading conclusions about a drug's efficacy, safety, and tolerability, as well as significant financial implications. Digital pill technologies enable the tracking of medication adherence through an embedded sensor that links to an external device. This innovation addresses challenges such as privacy concerns, regulatory compliance, and the need for patient education. The primary focus is on how digital pills are reshaping medication adherence, fostering a more transparent and efficient healthcare system.

Keywords: Digital Pill; Ingestible Sensor; Medication Adherence; Smart Pill; Clinical Trials**.**

1. Introduction

In the evolving healthcare system, digital health technologies play a key role in driving progress. The WHO emphasizes their global importance for future health. These innovations enhance health promotion, global security, and service delivery to at-risk populations. Among them, digital pills are particularly notable [1]. In November 2017, the Food and Drug Administration (FDA) granted its initial approval for a digital form of the second-generation antipsychotic aripiprazole, which includes an ingestible digital tracker [2]. These pills contain sensors that monitor pharmacotherapy through devices like smartphones, addressing patient non-compliance, a major challenge in healthcare leading to medication discontinuation [1]. Over one-third of the global population lives with at least two chronic illnesses, resulting in a greater demand for long-term healthcare [3]. Digital pills improve treatment adherence and help manage mental health and behavioural disorders like schizophrenia, bipolar I disorder, ADHD, substance abuse, smoking, pain, and insomnia. Researchers are also investigating their use for conditions such as cardiovascular diseases, diabetes, hepatitis C, AIDS, cancer, tuberculosis, and post-surgical opioid monitoring. This technology is especially valuable where patient behaviour affects medication compliance, including among the elderly and in neurodegenerative diseases [1].

A major advancement in digital medicine is the development of digital pills (DP)—innovative drug-device systems designed to collect and transmit personal health data, especially for monitoring medication adherence and health behaviours. As shown in Figure 1, digital pills include three main components: an ingestible sensor, a wearable patch, and a mobile app connected to an external web server [4]. A current Digital Pill System (DPS) includes an ingestible electronic sensor within a standard gelatin capsule, paired with a wearable patch or receiver. This setup integrates the

* Corresponding author: S P Hiremath

medication and sensor, effectively transforming the capsule into a digital pill [5]. The ingestible sensor, activated by stomach acid, sends signals to a wearable patch on the patient's abdomen. The patch collects sensor data and physiological indicators like heart rate and activity, transmitting it to a mobile app and online portal for access by the patient, family, and healthcare providers. Digital pills work with traditional medications to enable accurate tracking of adherence and health metrics [4]. They are designed for ease of use and automatically monitor adherence, reducing the need for individuals to actively report their adherence data [6].

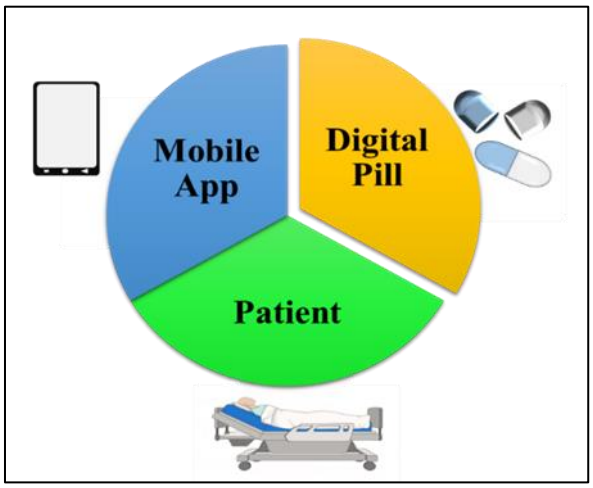

Figure 1 Process of Digital Medicine System.

Many healthcare professionals favour "adherence" over "compliance" because "compliance" implies passive obedience, ignoring the collaborative patient-provider relationship. Still, both terms may present a limited and potentially misleading view of medication-taking behaviour [7]. Using terms like "adherence" or "compliance" for missed doses can stigmatize patients in future care. While it's important to rethink how we describe medication-taking behaviour, these terms are still widely used. Ultimately, patients benefit most when they follow prescribed regimens closely [8].

According to WHO (2003), medication adherence is how well a person's behaviour aligns with agreed healthcare recommendations. Unlike compliance, which emphasizes obedience, adherence supports a collaborative approach respecting patient preferences. Persistence refers to the duration of therapy. Together, they define medication-taking behaviour and guide how digital tools can improve adherence [9].

Ingestible biosensors enable real-time medication adherence monitoring, aiding HIV patients using stimulants. However, high costs, privacy concerns, safety, efficacy, and patent issues hinder widespread adoption of digital pills in healthcare [7].

Overestimated medication adherence in clinical trials can skew results and increase costs. Digital pills ensure accurate adherence tracking, improving reliability and efficiency in both early and later-phase trials for better outcomes [10].

This study evaluates digital pill systems' impact on medication adherence, health outcomes, and data collection in clinical trials, addressing challenges like cost, privacy, safety, and their role in chronic disease management.

1.1. Historical Overview

Digital pills, classified as "Digital Therapeutics," contain sensors that communicate with devices like smartphones. The concept started in 1957, with significant progress in the 1990s. Proteus Digital Health developed a digital pill that activates in stomach acid, transmitting data to a smartphone. This technology aims to improve medication adherence in conditions like schizophrenia, though it raises paranoia concerns. Dr. Norman H. Payson proposed digital pills in the 1970s, and in 2001, MIT created the first functional ingestible sensor for detecting gastrointestinal bleeding.

In 2010, the FDA approved the first digital pill, Abilify MyCite, which includes an embedded sensor to track medication adherence in individuals with mental health disorders. It was developed by Otsuka Pharmaceutical in collaboration with Proteus Digital Health [11]. The FDA's approval of Abilify MyCite has been seen as a "landmark" event. Since then, several companies, like etectRx and Medimetrics, have developed digital pills for medication adherence, disease management, and clinical research. Despite their potential to improve healthcare, digital pills raise ethical and privacy

concerns regarding patient data collection, limiting their adoption. The long-term impact of these technologies on healthcare remains uncertain [13]. Chevance et al. (2022) argue that digital pills should be seen not just as an innovative medication delivery method, but as a complex intervention that requires thorough testing before widespread clinical use. They stress the importance of a strong ethical and legal framework to ensure responsible and appropriate use of these medications [14].

1.2. The technology behind the digital medicine system

Technology plays a crucial role in various sectors and daily life, with healthcare innovations, particularly in manufacturing technologies, being vital for improving and safeguarding lives worldwide. This integration has a significant impact on global health outcomes [15]. Digital pills revolutionize healthcare by merging pharmacology with technology, transmitting health data to doctors or smartphones, enhancing medication adherence, monitoring health, and improving the management of internal conditions [7]. Developing innovative drug delivery systems and control mechanisms is vital for advancing next-generation technologies [16]. Digital pills effectively address medication non-adherence, a major challenge in efficient healthcare management [17]. Recent healthcare advances integrate consumer technologies and automation into medical devices, addressing network, security, and compatibility issues, and making medicine increasingly central to the healthcare system [18].

The Digital Medicine System updates prescriptions via smartphone or electrochemical sensing technology [19]. Designing macro-devices for oral drug delivery requires prioritizing ease of swallowing, guided by FDA recommendations on the size, shape, and physical attributes of capsules and tablets [20].

Digital medicine features an ingestible sensor made from dietary minerals like copper, magnesium, and silicon. The sensor has three main components: the active layer, integrated circuit, and insulated skirt disk.

The integrated circuit, a miniature semiconductor, is about the size of a food particle. Using magnesium and copper electrodes provides an ideal balance of power, biocompatibility, microfabrication ease, and cost-effectiveness. The minerals released are well below typical dietary levels, and the sensor is incorporated into each tablet or capsule during manufacturing [21].

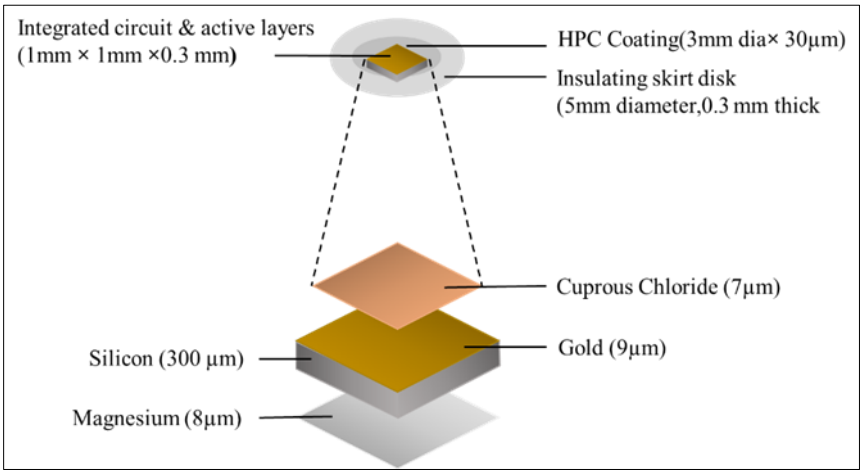

Figure 2 A diagram of the ingestible sensor, along with a cross-sectional illustration detailing its individual components

Once the sensor contacts gastric fluids after ingestion, it transmits a unique, secure digital code that identifies the medication, its dosage, and a timestamp. The sensor operates without needing an external battery, antenna, or radio frequency transmission, as it harnesses power directly from the human body [21]. The intestine absorbs minimal copper and magnesium from the ingestible sensor, far below daily intake recommendations. The 10 cm patch tracks medication ingestion times and dates, with a foam layer for secure adhesion and water resistance. Worn on the upper torso, it can withstand most activities but requires adhesive replacement weekly due to loosening from vigorous activity or prolonged water exposure [19].

When paired with a wearable sensor patch and a mobile app, the sensor enables near real-time, continuous tracking of medication adherence. Additionally, the digital medicine program establishes a direct link between medication usage,

health-related behaviours like physical activity, and clinical metrics such as heart rate and sleep patterns [21]. Refer to Figure 3: for an overview of the DMO.

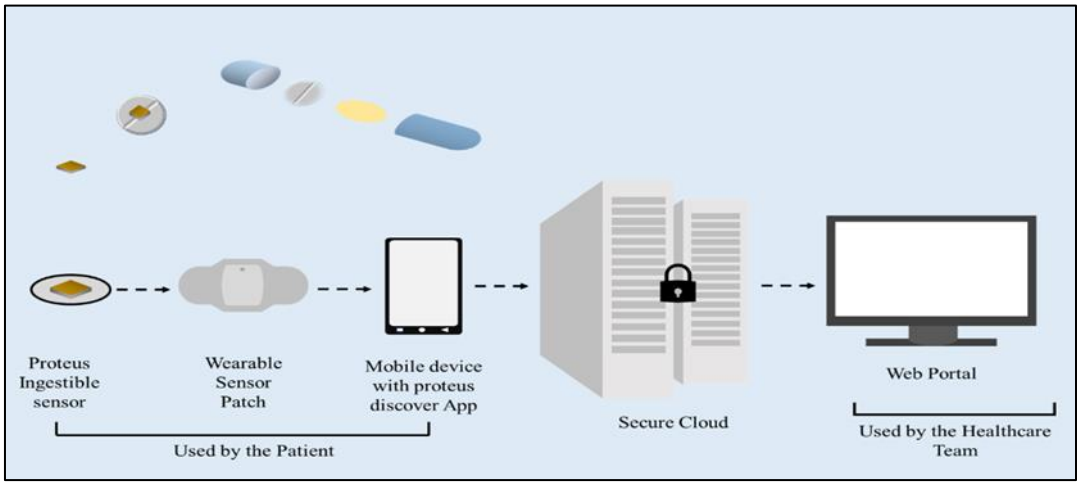

Figure 3 Top left: Ingestible sensor and pill. Top right: Co-encapsulation of medication within the ingestible sensor pill. Bottom: Components of the DMO system and data flow

1.3. Parts of digital pills

Ingestible sensors and capsules must be designed for easy swallowing and retention. Digital pills typically include sensors, receivers, mobile devices, cloud servers, and software to track medication adherence and improve outcomes. This section covers the requirements for reliable, long-lasting devices [13].

- **Sensors:** Digital pills contain sensors that, integrated with software on devices like computers and smartphones, track medication effectiveness. These sensors collect and transmit data for analysis, detecting physical and chemical properties within capsules. The application section will cover different types of sensors in digital pills, including optical, electrochemical, and temperature sensors, along with their driver units [13].
- **Microcontrollers and processors:** Microcontrollers and processors work together to make digital pills effective. Microcontrollers manage tasks like data transfer and environmental monitoring, while processors interpret the data and provide real-time insights. This collaboration allows digital pills to track adherence, alert patients about missed doses, and identify absorption issues, making them a powerful tool for improving medication management and patient outcomes [13].
- **Telecommunication:** Telecommunication is crucial in sensor-embedded pills as it enables wireless data transmission to devices for analysis and monitoring. The following points explain its use in these pills [13].
- **Wireless transmission:** Near-field communication (NFC) chipsets work within a few centimetres, while BLE chipsets offer wireless connectivity over several meters, enabling real-time monitoring with devices like smartwatches and smartphones. The system uses the TI CC2541 BLE System-on-Chip for communication and processing, along with the LMP91000 AFE, controlled via an I2C interface by the CC2541 [22].
- **Data encryption:** Tablets with integrated sensors use encryption techniques, such as AES or DES, to protect data privacy and prevent unauthorized access or interception during transmission [13].
- **Remote monitoring:** Telecommunications enable remote patient monitoring, providing healthcare professionals real-time access to patient data via wireless networks for faster interventions and improved health outcomes [13].
- **Data storage:** Medications with sensors transmit data to cloud-based systems for storage and analysis. Large-scale data analysis and machine learning help identify health trends, enabling more personalized treatments [13].

1.4. Power Supplies

When specifying a power supply system, key factors include power density, energy density, and battery capacity. Batteries serve as the primary internal power source, with external options such as wireless power transfer via magnetic induction or energy harvesting from natural sources [23]. Batteries face challenges at the mesoscale, as smaller batteries in robotic capsules often lack sufficient energy density for extended operation. Lithium-ion polymer

(LiPo) batteries are preferred for these systems due to their ability to deliver peak currents up to 20 times their rated current, flexibility, and ease of positioning within capsules [24].

Commercial capsules typically use silver oxide coin batteries, providing 8–10 hours of operation at 3V, 55 mAh, and 20 mW power. However, lithium-ion (Li-ion) batteries offer a viable alternative with a higher energy density of around 200 Wh/kg [23]. Wireless energy transfer via induction is limited by the body's weakening magnetic field. Alternative methods like electric-field induction, radio waves, microwave radiation, and piezoelectric ultrasound may enable smaller nano systems for optoelectronics, biosensors, and resonators [25].

1.5. Drug release mechanism

Drugs can be delivered through passive or active mechanisms. In passive systems, the drug is released via diffusion or chemical reactions driven by factors like temperature or pH at the targeted site. In active systems, the capsule actively releases the drug from a reservoir when triggered [26].

Passive release mechanism: In the 1980s, the Battelle Institute in Frankfurt developed the first swallowable drug delivery capsule, the HF capsule. Activated by RF signals, it melted a thread, releasing a needle to puncture a balloon and passively deliver the drug through the capsule wall [23, 27].

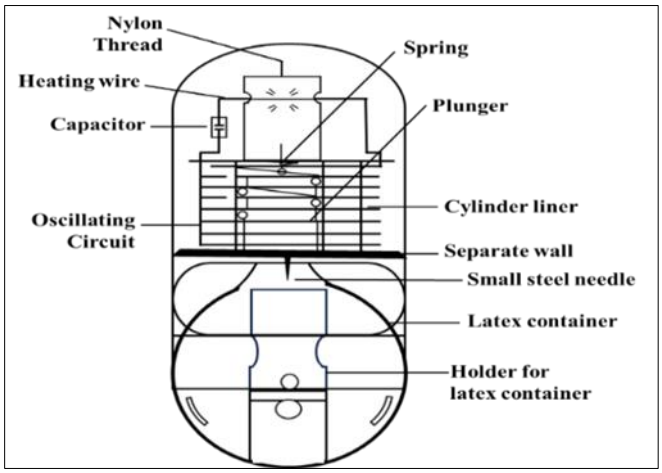

Figure 4 The HF capsule, developed by Battelle Institute in Frankfurt am Main, Germany, was activated by an RF signal

InteliSite, Enterion, and HF Capsule are prototype models developed for drug delivery purposes [28]. The InteliSite® capsule (Innovative Devices, Raleigh, NC, USA) is widely used for non-invasive absorption studies. Measuring 10 mm in diameter and 35 mm in length, it features a 0.8 ml drug reservoir, onboard electronics, housing, and an actuator system. The capsule's outer and inner sleeves each have six slots arranged in two rows of three. When the inner sleeve rotates, the aligned slots allow passive drug release. Figure 5 shows the capsule's components.

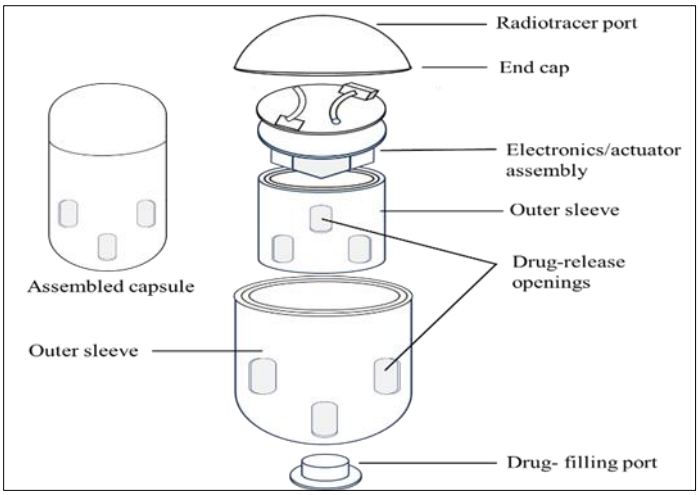

Figure 5 The InteliSite® capsule made up of a housing assembly, an embedded electronics and actuator system, and a drug reservoir that holds 0.8 ml

The Magnetic Active Agent Release System (MAARS) by Matesy GmbH uses magnetic fields for targeted drug delivery. A magnetic carrier holds the drug and stays sealed during transport thanks to a wall made of semi-hard and soft magnetic materials. Once at the target site, an external magnetic field triggers the capsule to open, releasing the drug in powder or liquid form. The capsule's total volume is 0.847 ml, with a 0.34 ml drug reservoir [26].

1.6. Active release mechanism

Active release mechanisms offer precise drug delivery, often using pistons for controlled release from the reservoir. To improve chemically-based systems, the IntelliCap system was developed by Philips Research. This swallowable capsule includes a drug reservoir, sensors for pH and temperature, a piston powered by an electromotor, a programmable microprocessor, and a wireless transceiver. The system enables real-time monitoring of temperature and pH, with the stepper motor remotely activated to release the drug into the gastrointestinal tract. Figure 6 shows the IntelliCap system [27, 23, 26, 30].

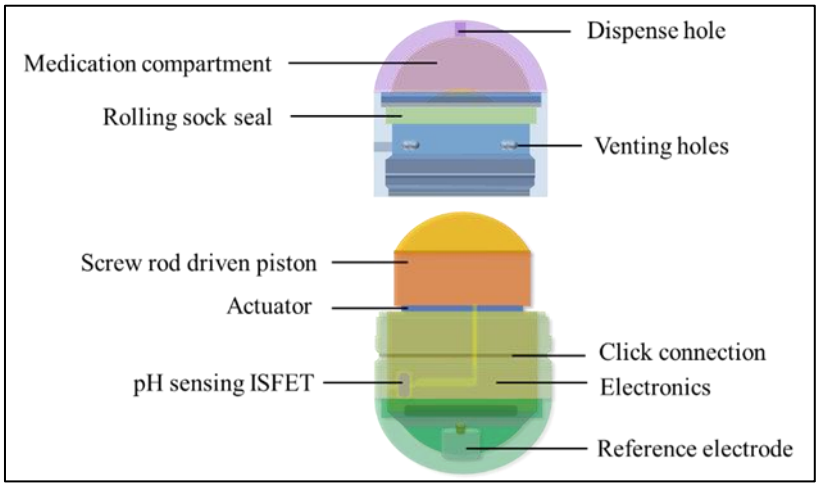

Figure 6 The IntelliCap developed by Philips Research is activated by pH measurement

The IntelliCap system encapsulates a drug formulation, protects it from the gastrointestinal environment, and releases it accurately at a targeted site via a bolus or extended-release strategy [31]. Its size is similar to other wireless capsule endoscopy devices, including the Given Imaging SB (Given Imaging, Yoqneam, Israel), Endocapsule (Olympus, Tokyo, Japan), and Smart Pill (Smart Pill, Buffalo, NY, USA) [30]. The pill can deliver its full dose in about 10 minutes for a burst release or slowly over a longer duration. The medication compartment holds 300 µl, and pH sensors in the gastrointestinal tract monitor the release process for personalized treatment [26].

Woods et al. developed a precise drug delivery platform with a medication reservoir and a needle positioning mechanism to accurately target specific sites. The device holds up to 1 ml of medication, about one-third of its total volume [23].

The Magnetically Actuated Soft Capsule Endoscope (MASCE) delivers drugs by compressing a 0.17 ml chamber using internal and external magnets. Once the pressure threshold is met, the drug is released through small openings. It supports multiple doses with controlled release but requires precise magnet alignment within 100 mm for effective operation [26].

The Enterion capsule by Phaeton Research (Nottingham, UK) targets drug delivery in the GI tract. Measuring 32 mm in length, it holds up to 1 ml of powder or liquid and features a 9 mm opening sealed with a push-on cap and silicone O-ring for secure closure [29]. Gamma-scintigraphy is widely used to develop and evaluate drug delivery systems, especially for tracking formulations in the gastrointestinal and respiratory tracts. It involves radiolabelling with agents like technetium-99m or indium-11132. The capsule activates in the intestine via an external magnetic field, powering a coil that heats a filament. The filament melts, releasing the drug through a 9 mm opening. The O-ring cap detaches, and a spring stores 0.18 joules of energy. A switch sends a radio signal to confirm drug release [29].

Table 1 Drug release methods

Device	Capsule Dimensions	Drug reservoir volume	Mechanical release mechanism	Powered by
HF Capsule	-	-	Passive	-
InteliSite	35×10mm	0.8ml	Passive	Battery
MAARS	18.2×7.7mm	0.34ml	Passive	Battery
IntelliCap	26×11mm	3ml	Active	Battery
MASCE	15×40mm	0.17ml	Active	Magnetic field
Enterion	32×10mm	1 ml	Active	Magnetic field

Introduced in 2004, the PillCam ESO is a video capsule for imaging the oesophagus, equipped with cameras on both ends and capturing 14 frames per second. It's easy to swallow and similar in size to a multivitamin. The PillCam Colon (PC) capsule is used for polyp surveillance and colorectal cancer monitoring in high-risk individuals [33].

1.7. Adherence to medication

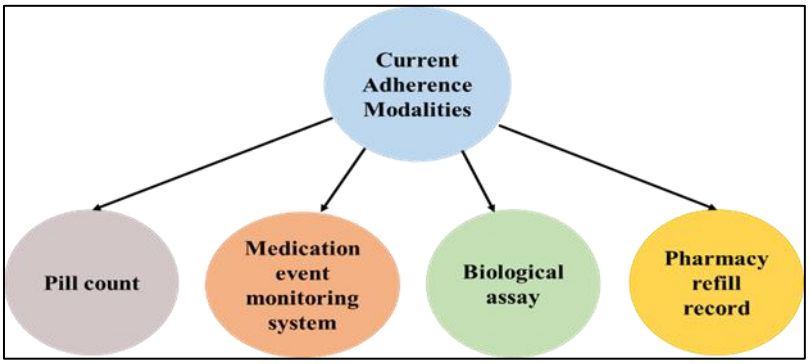

Figure 7 Current approaches to monitoring adherence

Adherence is a sophisticated concept that encompasses meanings beyond its simple definition. Klugman and colleagues define adherence as “the degree to which a patient follows medical advice, most commonly with regard to taking medications” [34, 19]. Improving medication intake monitoring and adherence can lead to better compliance [35]. Digital medicine sensors enhance medication adherence, with some products already approved. For instance, Rush University is working with a pharmacy to embed Proteus Digital Health’s ingestible sensor into existing drugs. Otsuka Pharmaceuticals recently gained FDA approval to pair this sensor with Abilify (aripiprazole) for treating mental health conditions [19]. The ID-Cap System by etectRx uses an embedded sensor to track medication adherence. Supported by

the FDA, it aligns with the Digital Health Innovation Action Plan to advance technological solutions that improve patient adherence [37]. Current adherence methods are shown in Figure 7.

Digital pills play a key role in addressing medication non-adherence, a major challenge in healthcare. Non-adherence disrupts healthcare systems, and patients are considered adherent if their medication intake-to-prescriptions ratio is 80% or higher [17]. The World Health Organization's "Adherence to Long-Term Therapies: Evidence for Action (2003)" report examines nine chronic conditions, including asthma, cancer (especially in palliative care), depression, diabetes, epilepsy, HIV/AIDS, hypertension, tobacco cessation, and tuberculosis, highlighting the importance of adherence in managing these conditions [38].

1.8. Non-adherence to medication

Patients can be fully adherent, partially adherent, or non-adherent. Research indicates that non-adherence is linked to nearly 50% of treatment failures, resulting in approximately 125,000 deaths and 25% of hospitalizations annually in the United States [39]. Medication adherence for chronic conditions is around 50%, with half of individuals with psychotic disorders not following prescribed antipsychotic treatments, despite the availability of effective medications for psychiatric disorders [40].

Non-adherence is influenced by factors such as patient behavior, illness severity, treatment complexity, medications, ADRs, social and economic factors, patient-provider relationships, follow-up care, and healthcare system dynamics. Figure 8 highlights these diverse determinants of non-adherence.

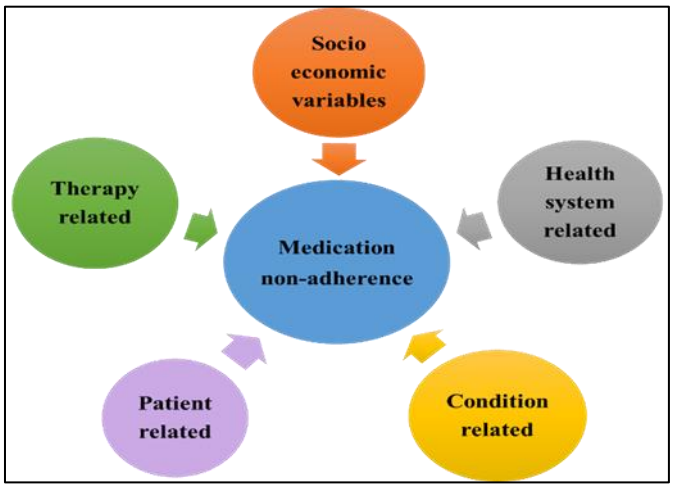

Figure 8 Various factors influencing medication non-adherence

Non-adherence is influenced by poor patient-provider relationships, communication, complex treatment plans, system challenges, and lack of education, leading to complications and higher mortality rates [9, 41].

1.9. Approaches to enhance medication adherence

Monitoring and improving adherence can provide significant health and economic benefits. Patients with chronic conditions often face challenges with adherence. Effective strategies involve collaboration and may include single or combined interventions over time to enhance patient outcomes [39]. The Figure 9: illustrates various approaches designed to enhance medication adherence.

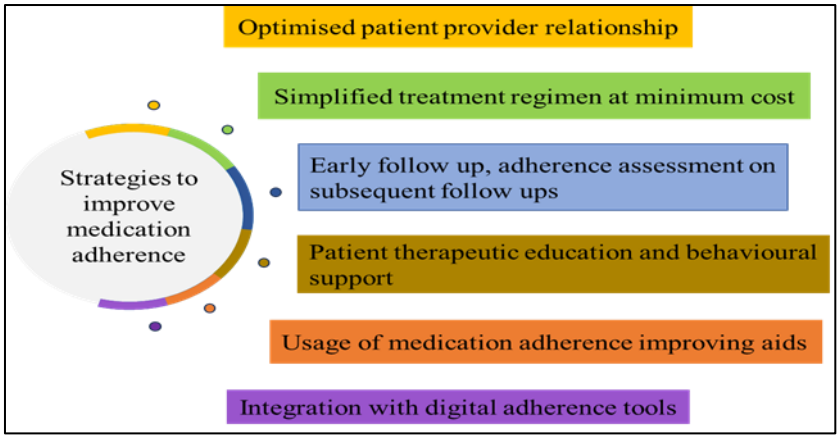

Figure 9 Approaches to enhance medication adherence

Treatment adherence involves active patient-clinician collaboration in medication decisions, unlike passive compliance. Persistence refers to how long a patient continues the prescribed treatment [42]. Patient education and behavioural interventions improve adherence by addressing concerns, promoting healthy lifestyles, and supporting positive treatment beliefs for better outcomes [43]. Advancing healthcare technology introduces digital tools, from reminders to smart pills and integrated devices, improving adherence.

2. Technology-based approaches to improve medication adherence

Technologies are essential in healthcare, improving decision-making, connections, and system efficiency. The WHO recommends combining digital health interventions (DHIs) with system improvements like telehealth and SMS reminders [44]. Efforts to reduce disease burden and healthcare costs aim for a 25% reduction in hypertension by 2025, as per WHO. Strategies include integrated management of hypertension, diabetes, and other risks in primary care, along with education and promoting medication adherence.

Medication storage devices with cellular technology now enable real-time tracking of adherence. Research in China has studied the impact of triggered phone reminders and counselling, guided by adherence data, on ART adherence in HIV patients [45]. The following section explores digital approaches to improving medication adherence.

2.1. Radio frequency identification

Radio frequency identification (RFID) uses radio waves for unique object identification, consisting of a tag and a reader. In healthcare, it aids in billing, inventory management, drug safety, counterfeit prevention, and medication adherence. RFID tags on medication labels and containers ensure correct treatment administration [46, 47].

2.2. Near Field Communication

Near Field Communication (NFC) builds on RFID, allowing bidirectional communication between compatible devices like tags and smartphones. NFC tags store data on small chips and can be integrated into formats such as stickers, labels, and packaging [48]. Smartphones read NFC data to track medication use through labels, packaging, and devices, aiding caregivers and pharmacies. NFC tags on devices offer guides, information, and videos to improve patient adherence [49, 9].

2.3. MHealth and mobile health application

mHealth uses mobile technology in healthcare to collect data, helping patients access information and enabling providers to obtain clinical details, improving decision-making in clinical settings [50]. mHealth uses mobile devices and wearable sensors to monitor wandering behaviour. A study developed an integrated system with a patient app and provider dashboard to manage type 2 diabetes in pregnant Medicaid participants using a user-centered design [50]. The growth of social networks and smartphone apps has transformed communication, with 79% of Spaniards owning smartphones by 2018. This shift is also reshaping healthcare, as the Internet and mHealth transform traditional models [52]. Digital tools collect health data, empowering self-management, improving adherence, and enhancing care quality for professionals [54].

2.4. Smart Blister design

A replica valsartan blister pack with a Smart Blister label was designed, logging pill dispensing data via RFID and NFC, and transferring it to an Internet database through a GPRS-enabled reader [55]. Smart Blisters use patient IDs for accurate data collection and scanning at refills to monitor adherence and dosing behaviour graphically.

2.5. Smart pill bottles

Smart pill bottles monitor adherence using cap sensors to detect openings and bottle sensors to measure pill weight. Though user-friendly, they are costly and not definitive. Studies show improved adherence in multiple myeloma patients and breast cancer survivors, especially when combined with pharmacist interventions or mobile app connections [56].

2.6. Medication event monitoring system (MEMS)

The Medication Event Monitoring System (MEMS) uses a microprocessor-equipped bottle cap to record each opening's time and frequency. It has been applied across various patient groups, with one study focusing on veterans with chronic mental health disorders receiving intensive support in a day hospital setting [57].

2.7. Smart Drawers

Smart drawers or radio-frequency identification (RFID)-based medication drawer [58]. Smart drawers scan medications, detect drawer activity, and use IoT to track usage with timestamps, improving adherence monitoring and alerting patients and caregivers when treatment protocols are missed, enhancing outcomes [60, 9].

2.8. The Impact of Non-Adherence on Clinical Trials

Medication adherence in clinical trials is often overstated, leading to misleading results, suboptimal outcomes, increased development costs, and reduced trial effectiveness due to unrecognized inconsistent dosing by participants [61]. An analysis of 95 clinical trials with 16,907 participants showed a steady decrease in medication adherence over time. By day 100, 80% of participants adhered to the schedule, and after one year, 40% had discontinued their medication completely [62].

2.9. How Digital Pills Can Be Integrated into Clinical Trials:

Some readers might question: why choose a digital pill over other adherence tracking methods? Is it challenging to implement a digital pill? What types of studies are best suited for the use of a digital pill?

In clinical research, methods like self-reports, mobile apps, pill counts, and electronic dispensers track medication adherence. However, these methods often lack optimization and reliability, with issues in data accuracy, integrity, and completeness, reducing their effectiveness in clinical studies [63]. In early-phase trials, such as pharmacokinetic and dose-finding studies, strict adherence is crucial. Unreliable results can jeopardize dosing accuracy, impacting drug safety, effectiveness, and the overall drug development process [10]. In pivotal trials, strict adherence ensures reliable ITT analyses by linking outcomes to adherence levels [64].

3. Limitations

- **Geographical Scope:** The study's geographic limitation may affect digital pill acceptance, highlighting the need for context-specific research [65].
- **Healthcare Professional Sample Bias:** The sample of healthcare professionals was not representative of the larger healthcare workforce.
- **Language Barrier**: The study excluded non-English speakers; future research should include their responses to Digital Pill System (DPS) technology [66].
- **Potential Barriers for Other Populations**: Digital Pill System (DPS) operation may challenge individuals with limited tech experience or no smartphone access [67].

3.1. Applications

- **Medication Adherence Monitoring:** Digital pills track medication adherence, helping improve treatment outcomes.
- **Chronic Disease Management:** They help manage diabetes, hypertension, and heart failure by tracking medication intake and patient behaviour.
- **Personalized Medicine**: Digital pill data enables personalized treatment based on individual needs and conditions [58].
- **Cost Reduction in Healthcare**: Digital pills minimize drug doses, support providers and patients, and significantly reduce overall healthcare costs [68].
- **Manufacturing Technologies by 3D Printing**: Silicon, PCB, and microfabrication technologies enable production of advanced, high-performance electronic devices [69].
- **Targeted Drug Delivery:** Digital pills like (e.g. MAARS) precisely target GI regions to study and customize drug absorption profiles [70].

4. Conclusion

The future of medication adherence is evolving with digital pills, revolutionizing tracking, monitoring, and patient engagement. These pills provide valuable data for personalized treatment, reduce healthcare costs, and improve outcomes by addressing non-adherence. Despite challenges like data privacy and accessibility, collaboration among developers, healthcare professionals, and policymakers is essential. By prioritizing user experience and education, digital pills will empower patients, standardize adherence, and significantly enhance healthcare quality, benefiting both individuals and communities.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Litvinova O, Klager E, Tzvetkov NT, Kimberger O, Kletecka-Pulker M, Willschke H, et al. Digital Pills with Ingestible Sensors: Patent Landscape Analysis. Pharmaceuticals. 2022;15(8):1–19.

[2] El Hadidi S, Rosano G. Evidence beyond the digital medication pill. Eur Hear J - Cardiovasc Pharmacother. 2020;6(2):72–4.

[3] Chevance A, Fortel A, Jouannin A, Denis F. Acceptability of and Willingness to Take Digital Pills by Patients , the Public , and Health Care Professionals : Qualitative Content Analysis of a Large Online Survey Corresponding Author : 2022;24:1–19.

[4] 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 Med Ethics. 2020;21(1):1–13.

[5] Chai PR, Goodman G, Bustamante MJ, Mohamed Y, Castillo-Mancilla J, Boyer EW, et al. Long-Term Stability of the Electronic Sensor Component of a Digital Pill System in Real-World Storage Settings. J Pharm Technol. 2021;37(3):135–9.

[6] Chai PR, Carreiro S, Innes BJ, Rosen RK, O'Cleirigh C, Mayer KH, et al. Digital pills to measure opioid ingestion patterns in emergency department patients with acute fracture pain:a pilot study. J Med Internet Res. 2017;19(1):1–10.

[7] Yasmin R, Sarkar A, Bhattacharyya S, Majumder A, ... Smart Pills and Ingestible Sensors for Real-Time Health Monitoring: A Patient Landscape and Over View. ResearchgateNet. 2024;13(06).

[8] Kaleva V. Adherence to medication. Pediatriya. 2015;55(2):68–9.

[9] Setya S, Singh MF, Talegaonkar S. Bulletin of Environment, Pharmacology and Life Sciences Digital Technology for Improvement of Medication Adherence. Env Pharmacol Life Sci. 2022;(November):230–8.

[10] Klein GL. The Case for Digital Pill Use in Clinical Trials. Clin Trials Pract – Open J. 2021;4(1):16–21.

[11] Swartz AK, Friesen P. The First Smart Pill: Digital Revolution or Last Gasp Kennedy Inst Ethics J. 2023;33(3):277–319.

[12] Diedericks H. Digital Pills and Promises. 2019;63–7.

[13] Chaurasiya V. A New Era in Medication Monitoring : Sensor Embedded Digital Pills CamScanner. 2024;(June 2023).

[14] Litvinova O, Klager E, Yeung AWK, Tzvetkov NT, Kimberger O, Kletecka-Pulker M, et al. Bibliometric analysis and evidence of clinical efficacy and safety of digital pills. Front Pharmacol. 2023;14(January):1–14.

[15] Sahoo S, Bagjadab AB, Priyadarshini SBB. Smart pills: A complete revolutionary technology than endoscopy. Emergence of Pharmaceutical Industry Growth with Industrial IoT Approach. Elsevier Inc.; 2019. 275–303 p.

[16] Fesseha H, Degu T. Archives of Clinical Case Reports Smart Drug Delivery System : A Review. 2022;(August).

[17] De Miguel Beriain I, Morla González M. "Digital pills" for mental diseases: An ethical and social analysis of the issues behind the concept. J Law Biosci. 2020;7(1):1–19.

[18] Dayananda P, Upadhya AG. Development of Smart Pill Expert System Based on IoT. J Inst Eng Ser B. 2024;105(3):457–67.

[19] K SS, M SK, A RP. Digital Pills: Impact of Rising Technology. Arch Med. 2021;13(6):26.

[20] Milián-Guimerá C, McCabe R, Thamdrup LHE, Ghavami M, Boisen A. Smart pills and drug delivery devices enabling next generation oral dosage forms. J Control Release. 2023;364(June):227–45.

[21] Plowman RS, Peters-Strickland T, Savage GM. Digital medicines: clinical review on the safety of tablets with sensors. Expert Opin Drug Saf. 2018;17(9):849–52.

[22] Kim J, Imani S, de Araujo WR, Warchall J, Valdés-Ramírez G, Paixão TRLC, et al. Wearable salivary uric acid mouthguard biosensor with integrated wireless electronics. Biosens Bioelectron. 2015;74:1061–8.

[23] Goffredo R, Accoto D, Guglielmelli E. Swallowable smart pills for local drug delivery: Present status and future perspectives. Expert Rev Med Devices. 2015;12(5):585–99.

[24] Gorlewicz JL, Webster RJ, Valdastri P. Mesoscale mobile robots for gastrointestinal minimally invasive surgery (MIS). Med Robot. 2012;224–51.

[25] Wang ZL, Song J. Piezoelectric nanogenerators based on zinc oxide nanowire arrays. Science (80-). 2006;312(5771):242–6.

[26] Biomedica I, Goffredo R, Goffredo R. Università Campus Bio-Medico di Roma School of Engineering PhD Course in Biomedical Engineering A swallowable smart pill for drug delivery into the gastrointestinal tract. 2015;(October).

[27] Cummins G. Smart pills for gastrointestinal diagnostics and therapy. Adv Drug Deliv Rev. 2021;177:113931.

[28] Jansen D, Fawaz N. A developed platform of smart electronic pill (ePille ®) using near field bidirectional communication system for biomedical telemetry application with drug delivery system ePille Design Concept. Forschung. 2014;(October):2–3.

[29] Wilding I, Hirst P, Connor A. Development of a new engineering-based capsule for human drug absorption studies. Pharm Sci Technol Today. 2000;3(11):385–92.

[30] Van Der Schaar PJ, Dijksman JF, Broekhuizen-De Gast H, Shimizu J, Van Lelyveld N, Zou H, et al. A novel ingestible electronic drug delivery and monitoring device. Gastrointest Endosc. 2013;78(3):520–8.

[31] Discovery D. Drug Discovery , Development & Delivery Smart Pills for Oral Drug Delivery. 2014;6(3):72–4.

[32] Davis SS, Hardy JG, Newman SP, Wilding IR. Gamma scintigraphy in the evaluation of pharmaceutical dosage forms. Eur J Nucl Med. 1992;19(11):971–86.

[33] Fireman Z, Kopelman Y. New frontiers in capsule endoscopy. J Gastroenterol Hepatol. 2007;22(8):1174–7.

[34] Swartz AK. Smart Pills for Psychosis: The Tricky Ethical Challenges of Digital Medicine for Serious Mental Illness. Am J Bioeth. 2018;18(9):65–7.

[35] Young MA, Dimartino L. Trackable pill digital technology in PRM & pain: Hype or hope Ann Phys Rehabil Med. 2018;61:e115.

[36] Baumgartner SL, Buffkin DE, Rukavina E, Jones J, Weiler E, Carnes TC. A novel digital pill system for medication adherence measurement and reporting: Usability validation study. JMIR Hum Factors. 2021;8(4):1–12.

[37] Sideri K, Cockbain J, Van Biesen W, De Hert M, Decruyenaere J, Sterckx S. Digital pills for the remote monitoring of medication intake: a stakeholder analysis and assessment of marketing approval and patent granting policies. J Law Biosci. 2022;9(2):1–38.

[38] Burkhart P V., Sabaté E. Adherence to Long-Term Therapies: Evidence for Action. J Nurs Scholarsh. 2003;35(3):207–207.

[39] Kini V, Michael Ho P. Interventions to Improve Medication Adherence: A Review. JAMA - J Am Med Assoc. 2018;320(23):2461–73.

[40] Straczkiewicz M, Wisniewski H, Carlson KW, Heidary Z, Knights J, Keshavan M, et al. Combining digital pill and smartphone data to quantify medication adherence in an observational psychiatric pilot study. Psychiatry Res. 2022;315:6–10.

[41] Arbuckle C, Tomaszewski D, Brown L, Schommer J, Morisky D, Parlett-Pelleriti C, et al. Exploring the relationship of digital information sources and medication adherence. Comput Biol Med. 2019;109:303–10.

[42] Greer JA, Amoyal N, Nisotel L, Fishbein JN, MacDonald J, Stagl J, et al. A Systematic Review of Adherence to Oral Antineoplastic Therapies. Oncologist. 2016;21(3):354–76.

[43] Costa E, Giardini A, Savin M, Menditto E, Lehane E, Laosa O, et al. Interventional tools to improve medication adherence: Review of literature. Patient Prefer Adherence. 2015;9:1303–14.

[44] Wechkunanukul K, Parajuli DR, Hamiduzzaman M. Utilising digital health to improve medication-related quality of care for hypertensive patients: An integrative literature review. World J Clin Cases. 2020;8(11):2266–79.

[45] Sabin LL, Bachman DeSilva M, Gill CJ, Zhong L, Vian T, Xie W, et al. Improving Adherence to Antiretroviral Therapy With Triggered Real-time Text Message Reminders. JAIDS J Acquir Immune Defic Syndr. 2015;69(5):551–9.

[46] Staaby Anna, Haddara Moutaz. Radio Frequency Identification (RFID) technology and patient safety: EBSCOhost. Dep Technol Kristiania Univ Coll 32 Christ Krohgs gate, 0186 Oslo, Norw . 2018;(September):6–7.

[47] Rosenbaum BP. Radio frequency identification (RFID) in health care: Privacy and security concerns limiting adoption. J Med Syst. 2014;38(3):1–6.

[48] Kataria G, Dhyani K, Patel D, Srinivasan K, Malwade S, Syed Abdul S. The smart pill sticker: Introducing a smart pill management system based on touch-point technology. Health Informatics J. 2021;27(4):1–14.

[49] Morak J, Schwarz M, Hayn D, Schreier G. Feasibility of mHealth and Near Field Communication technology based medication adherence monitoring. Proc Annu Int Conf IEEE Eng Med Biol Soc EMBS. 2012;272–5.

[50] Twilt M. mHealth applications are they the future or another burden for our patients mHealth. 2023;9(5):9–11.

[51] Gejibo S, Mancini F, Mughal KA. Mobile Data Collection: A Security Perspective. 2015. 1015–1042 p.

[52] Lorca-Cabrera J, Martí-Arques R, Albacar-Riobóo N, Raigal-Aran L, Roldan-Merino J, Ferré-Grau C. Mobile Applications for Caregivers of Individuals with Chronic Conditions and/or Diseases: Quantitative Content Analysis. Int J Med Inform. 2021;145.

[53] Research2Guidance. mHealth Developer Economics Survey 2017-18. 2018;(March):1–17.

[54] Kim Y, Lee B, Choe EK. Investigating data accessibility of personal health apps. J Am Med Informatics Assoc. 2019;26(5):412–9.

[55] Van Onzenoort HA, Neef C, Verberk WW, Van Iperen HP, De Leeuw PW, Van Der Kuy PHM. Determining the feasibility of objective adherence measurement with blister packaging smart technology. Am J Heal Pharm. 2012;69(10):872–9.

[56] Park HR, Kang HS, Kim SH, Singh-Carlson S. Effect of a Smart Pill Bottle Reminder Intervention on Medication Adherence, Self-efficacy, and Depression in Breast Cancer Survivors. Cancer Nurs. 2022;45(6):E874–82.

[57] Diaz E., Levine H.B., Sullivan M.C., Sernyak M.J., Hawkins K.A., Cramer J.A., et al. Use of the medication event monitoring system to estimate medication compliance in patients with schizophrenia. J Psychiatry Neurosci. 2001;26(4):325–9.

[58] Raijada D, Wac K, Greisen E, Rantanen J, Genina N. Integration of personalized drug delivery systems into digital health. Adv Drug Deliv Rev. 2021;176:113857.

[59] Raikar AS, Kumar P, Raikar G (Vedant) S, Somnache SN. Advances and Challenges in IoT-Based Smart Drug Delivery Systems: A Comprehensive Review. Appl Syst Innov. 2023;6(4):1–20.

[60] Becker E, Metsis V, Arora R, Vinjumur J, Xu Y, Makedon F. SmartDrawer. 2009;1–8.

[61] Vrijens B, Urquhart J. Methods for measuring, enhancing, and accounting for medication adherence in clinical trials. Clin Pharmacol Ther. 2014;95(6):617–26.

[62] Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: Insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Annu Rev Pharmacol Toxicol. 2012;52:275–301.

[63] Eliasson L, Clifford S, Mulick A, Jackson C, Vrijens B. How the EMERGE guideline on medication adherence can improve the quality of clinical trials. Br J Clin Pharmacol. 2020;86(4):687–97.

[64] Detry MA, Lewis RJ. The intention-to-treat principle: How to assess the true effect of choosing a medical treatment. Jama. 2014;312(1):85–6.

[65] Chevance A, Fortel A, Jouannin A, Denis F, Mamzer MF, Ravaud P, et al. Acceptability of and Willingness to Take Digital Pills by Patients, the Public, and Health Care Professionals: Qualitative Content Analysis of a Large Online Survey. J Med Internet Res. 2022;24(2).

[66] Chai PR, Kaithamattam JJ, Chung M, Tom JJ, Goodman GR, Hasdianda MA, et al. Formative Perceptions of a Digital Pill System to Measure Adherence to Heart Failure Pharmacotherapy: Mixed Methods Study. JMIR Cardio. 2024;8(1).

[67] Chai PR, Bustamante MJ, Goodman G, Mohamed Y, Najarro J, Sullivan MC, et al. A brief training program to support the use of a digital pill system for medication adherence: Pilot descriptive study. JMIR Form Res. 2021;5(4).

[68] Ilan Y. Improving global healthcare and reducing costs using second-generation artificial intelligence-based digital pills: A market disruptor. Int J Environ Res Public Health. 2021;18(2):1–12.

[69] Ma WC, Goh GL, Priyadarshini BM, Yeong WY. 3D printing and 3D-printed electronics: Applications and future trends in smart drug delivery devices. Int J Bioprinting. 2023;9(4).

[70] Dietzel CT, Richert H, Abert S, Merkel U, Hippius M, Stallmach A. Magnetic Active Agent Release System (MAARS): Evaluation of a new way for a reproducible, externally controlled drug release into the small intestine. J Control Release. 2012;161(3):722–7.