Review Article

DIGITAL HEALTH

DIGITAL HEALTH
Volume 10: 1–16

DOI: 10.1177/20552076241277441
journals.sagepub.com/home/dhj

Sage

Exploring the potential of digital therapeutics: An assessment of progress and promise

Patrizio Armeni[1], Irem Polat[1], Leonardo Maria De Rossi[2], Lorenzo Diaferia[2], Severino Meregalli[2] and Anna Gatti[1]

Abstract

Digital therapeutics (DTx), a burgeoning subset of digital health solutions, has garnered considerable attention in recent times. These cutting-edge therapeutic interventions employ diverse technologies, powered by software algorithms, to treat, manage, and prevent a wide array of diseases and disorders. Although DTx shows significant promise as an integral component of medical care, its widespread integration is still in the preliminary stages. This limited adoption can be largely attributed to the scarcity of comprehensive research that delves into DTx's scope, including its technological underpinnings, potential application areas, and challenges–namely, regulatory hurdles and modest physician uptake. This review aims to bridge this knowledge gap by offering an in-depth overview of DTx products' value to both patients and clinicians. It evaluates the current state of maturity of DTx applications driven by digital technologies and investigates the obstacles that developers and regulators encounter in the market introduction phase.

Keywords

Digital therapeutics, digital health, digital medicine, artificial intelligence, virtual reality, policy and regulation

Submission date: 20 December 2023; Acceptance date: 6 August 2024

Introduction

Digital therapeutics (DTx) are an emerging type of medical therapy. The Digital Therapeutics Alliance (DTA) formally defines DTx as "*evidence-based, clinically evaluated software to treat, manage, and prevent a broad spectrum of diseases and disorders.*"[1,2] These therapies can be delivered through a variety of technologies, including smartphones, tablets, computers, virtual reality (VR) headsets and videogame platforms powered by software algorithms.[3,4] A distinctive characteristic of DTx is that, to be classified as such, regulatory bodies have to review and approve both clinical evidence and real-world data to ensure efficacy and adherence to standards of safety and risk.[5,6] These requirements testify that DTx are considered as a "*digital*" version of traditional "*therapeutics,*"[1] where the active ingredient is not a molecule but a digital solution. An obvious consequence of this definition is that a digital solution *per se* is not a DTx unless a clinically meaningful effect is identified and measured with the same standards used for traditional therapeutics. Therefore, if compared to consumer health products (e.g. fitness trackers), DTx products directly deliver medical interventions to patients.

In recent research, DTx have been identified as a promising alternative to pharmacological treatments across various medical conditions, highlighting their potential to change current treatment models. For example, in the case of attention-deficit hyperactivity disorder (ADHD), DTx offer a new approach to management, with clinical evidence showing significant promise.[7] Additionally, DTx has been found to provide appealing alternatives in other domains, such as enhancing walking outcomes,[7] delivering cognitive behavioral therapy (CBT) for insomnia, and managing

[1]LIFT Lab, CERGAS GHNP Division, SDA Bocconi School of Management, Milano, Italy
[2]LIFT Lab, CERGAS GHNP Division, and DEVO Lab, Claudio Dematté Research Division, SDA Bocconi School of Management, Milano, Italy

Corresponding author:
Patrizio Armeni, LIFT Lab, CERGAS GHNP Division, SDA Bocconi School of Management, 20136 Milano, Italy.
Email: patrizio.armeni@unibocconi.it

Parkinson's disease,[8] among the others. For some conditions, DTx could become a standalone alternative to pharmacological interventions,[9] while for others they could be used to complement medication,[5,9] but in both cases the therapeutic effect should be clearly identifiable and measurable. Since DTx are considered one of the most innovative areas within digital health, startups around the world are working to develop and validate several DTx products, and regulatory bodies have also started to explore how to navigate regulatory pathways.[10]

Despite early evidence of the potential of DTx and the variety of solutions that are rapidly entering the commercial markets of the United States and Europe, benefits and challenges are only recently being systematically studied by academics, regulators, and market analysts. In fact, while there is a proliferation of novel DTx solutions, their true potential is still in the early stages of exploration, so that manufacturers, healthcare providers (HCPs), patients, and regulators may not fully grasp their opportunities and challenges. Specifically, there are several points that remain under researched and contribute to a lack of comprehensive understanding of the DTx phenomenon, impacts, and challenges.

We identified four main areas that require further investigation (Figure 1). First, the current regulatory landscape for DTx is notably unclear and insufficient, lacking a definitive framework that ensures usability and sustained adoption. Secondly, uncertainties regarding patient safety still exist, which hinder the integration of DTx into clinical practice. Third, there is insufficient evidence supporting DTx effectiveness and clinical impact, which further limits the broader adoption of these solutions. All this also extends to the propensity of patients, HCPs, and payers in embracing these therapeutic approaches. Last, considering that we face a high variability of technological solutions that might enable DTx, we lack a comprehensive picture of the technologies that are currently used to enable such therapies as well as the manners in which they support therapeutic treatments in different cases. Consequently, all the clinical, regulatory, and organizational open points need to be addressed considering their unavoidable interrelations with the technological enablers that make DTx possible.

Therefore, the ambiguity and uncertainty surrounding DTx suggests a lack of research that comprehensively analyzes this concept and its foundational building blocks, considering technological enablers, potential application fields, and the challenges that must be overcome to foster adoption. In response to this research gap, with this review paper, we aim to provide an overview of the value of DTx products for patients and clinicians, the maturity of DTx applications enabled by digital technologies, and the challenges that developers and regulators face during the go-to-market process. Specifically, we aim to address the following points: (1) What are the novel distinctive factors and peculiarities of DTx compared to other digital-enabled applications in the medical field? (2) What are the technologies involved in DTx interventions? (3)

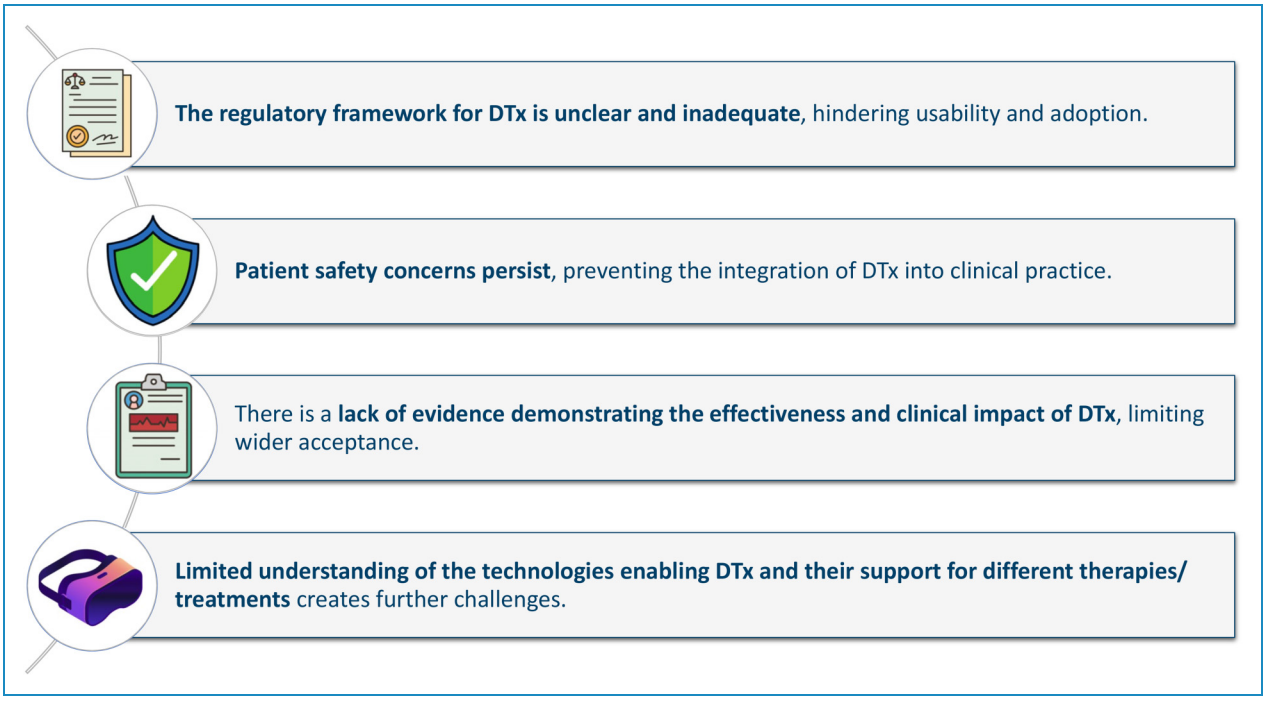

Figure 1. Key challenges to widespread adoption of DTx: four critical areas for further investigation.

What are the challenges faced by manufacturers, HCPs, patients and regulators? (4) How ready is the current regulatory landscape in different countries to allow DTx's diffusion?

In so doing, this paper contributes to the DTx literature and community in the following ways:

- **DTx conceptualization**. We clarify the definitions of DTx within other discussed areas of digital-enabled medical applications to underscore their boundaries and distinctions. This facilitates the establishment of clear definitions within the community, encouraging further studies in these areas. Furthermore, we present a comprehensive background, covering current applications and recent advances of DTx across diverse domains of healthcare.
- **Technological enablers.** We consolidate the DTx literature on the enabling technologies that support the DTx concept (i.e. mobile apps, artificial intelligence (AI), VR), accompanied by relevant clinical evidence. This consolidation is crucial considering the growing utilization of these technologies in DTx interventions, streamlining access for researchers and practitioners.
- **Challenges and strategies.** Lastly, we delve into regulatory, ethical, and other challenges hindering market adoption. Through discussion, we explore potential strategies to address these challenges and overcome the barriers they pose, offering insights for future developments in the DTx field. Finally, this paper invites the DTx stakeholders (MedTech and pharma companies, startups, payers, and government institutions) to work together to develop updated regulatory pathways and new access and reimbursement models for this class of software-based therapies.

Methods

In order to answer our research questions, in this paper we review articles from PubMed Central and ClinicalTrials.gov databases, as well as from Google Scholar search engine and global regulatory authority releases. Articles covered the period from 2015 to 2023. Databases were queried using the search terms that included a combination of ("digital therapeutics" OR "digital therapy") AND ("technology" OR "challenge" OR "regulation"). Initially, we chose the keyword "technology," as also discussed by Sverdlov et al.[10] to identify the most discussed technological enablers for the implementation of this treatment modality for patient care. Then, the keywords "challenge" and "regulation" were used to search for roadblocks during the go-to-market process as suggested by Patel and Butte.[5] In total, we analyzed 74 articles from journals and clinical trial reports, 13 sources from global authority releases (e.g. US Food and Drug Administration (FDA), The European Parliament) including DTA publications, and finally 1 DTx company report to support our findings.

Digital therapeutics: the state of the art

Key concepts and current applications of DTx

DTx are a type of product within the broader category of digital medicine, which is itself a subset of the larger field of digital health. Dang et al.[11] summarize these categories as described in Figure 2 and in the following paragraph.

Digital health is a broad term that encompasses various technologies, platforms, and systems designed to involve individuals in activities related to their lifestyle, wellness, and overall health. Digital health entities are capable of capturing, storing, and transmitting health data to assist with clinical operations. These systems include health information technologies, telehealth systems, tools that leverage consumer health information, clinical care management software, and various other types of digital health solutions. Digital medicine, instead, is a term used to describe software or hardware products part of Digital Health that are backed by evidence and are intended to measure or intervene in human health. It includes digital diagnostics, digital biomarkers, remote patient monitoring devices, DTx, and other similar products. Finally, as previously defined, DTx refer to evidence-based therapeutic interventions that are used to prevent, manage, or treat medical disorders or diseases. Consequently, DTx appear as a specific subcategory of Digital Medicine, within the broader field of Digital Health.

DTx can be delivered in a variety of digital formats that are accessible to patients, including smartphone applications, video games, VR programs, and other similar platforms.

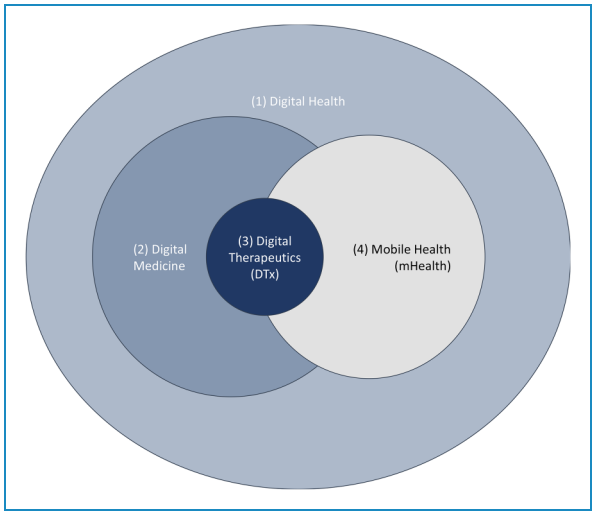

Figure 2. Definitions: digital health, digital medicine, digital therapeutics, and mHealth.

Advancements in technology and a growing trend toward personalized and participatory approaches to health have led to significant progress in the field of DTx in recent years. These developments have spurred the growth of DTx solutions and improved their accessibility to individuals seeking personalized care options.[11]

A part of DTx that are delivered through mobile technology can also be considered as falling within the adjacent field of mHealth. *mHealth* is a term used for medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices.[12] While DTx focus on specific therapeutic interventions for medical conditions, mHealth encompasses a wider range of health-related services and applications delivered through mobile devices. For instance, mHealth applications include the use of mobile devices in collecting community and clinical health data, delivery of healthcare information to practitioners, researchers, and patients, real-time monitoring of patient vital signs, delivery of training videos, meditation, or monitoring caloric intake for healthy weight maintenance.[13]

As a consequence of their complementary but different scopes, digital health, digital medicine, and DTx have varying requirements for clinical evidence and regulatory oversight. These differences arise due to varying levels of claims and associated risk levels.[14] In fact, DTx tend to be more sophisticated digital health products, which are now more akin to medicines rather than simple applications or apps. Moreover, given that a key characteristic of DTx is the delivery of a well-defined and measurable therapeutic intervention, such interventions can be assessed both in experimental and real-world settings to determine its impact as a stand-alone effect.

Given these peculiarities, Fürstenau et al.[13] highlight dimensions that distinguish DTx from other healthcare technologies as below:

1. **Specific medical purpose**: DTx are designed to address a specific medical condition and are not intended for general health purposes.
2. **Unique mechanism of action:** unlike the more general health and wellness purpose of mHealth apps, DTx have a specific mechanism of action that allows them to fulfill their medical purpose.
3. **Rigorous clinical evaluation**: DTx undergo rigorous clinical evaluations and are subject to regulatory oversight, similar to prescription drugs and other medical devices. Regulatory bodies review DTx based on clinical evidence to assess their efficacy, safety, and quality.
4. **Software-based therapies**: DTx leverage software-based technologies to deliver therapeutic interventions, therefore several technological aspects should be considered.
5. **Patient-directed or patient-provider-directed interventions:** the patient is the main user of a DTx application. Some may also be a combination of patient-and-physician-directed applications but DTx are not solely directed at providers.
6. **Apps on prescription**: Additionally, regulatory approval often enables HCPs to prescribe DTx to patients, further emphasizing their clinical relevance and medical nature.

So far, DTx have evolved as a complement of existing interventions (e.g. use of DTx in addition to medication-assisted treatment in opioid use disorder),[15] and in the future, in some cases, they might even become a full alternative to some of them. Herein, DTx are becoming an effective tool to remotely collect real-time data from patients through wearables and other sensors,[8] use data analytics and AI to understand patient's behavior and condition and communicate these conditions to HCPs to create more informed care plans.[16,17] These technology-enabled DTx services complement and add to the value of traditional healthcare delivery systems, and have the potential to deeply change not only patient experience,[11] but also patients' behaviors and, ultimately, the effectiveness of healthcare interventions. At the same time, DTx address some of the current issues of traditional healthcare systems, including the shortage and the burden on HCPs.[18] For example, a hypertension DTx app could educate patients on their lifestyle modification, including correcting their lifestyle habits and measuring daily blood pressure values, which allows physicians not only to obtain better results but also to objectively evaluate behavioral changes that occur in the patient's home via app, thus saving time and adopting prompter decisions.[19] This app can ease the burden on HCPs who might currently not have enough time to provide sufficient lifestyle guidance for each patient's effective hypertension management. While this case is an example of individual patient-level use, real-world outcomes generated by DTx may also be used for optimizing outcomes at the population level. Indeed, data can be aggregated and used to track progress or compare outcomes based on patient disease state, level of acuity, age, and gender.[2,20] This might generate more general benefits, as healthcare systems typically collect more data on process and output than on behaviors and outcomes.

To deliver these results, DTx can leverage a potentially large pool of enabling digital technologies. According to the study performed by Santoro et al.,[4] the majority of DTx interventions (41.9%) are currently delivered through mHealth applications. This is followed by web-based systems (25.7%), videogames (8.8%), VR (4.4%), text messages (3.7%), and others. In addition, growing debate is considering the convergence between DTx and more advanced digital technologies, such as AI, analytics,

and VR. Despite these initial efforts, the extent to which these technologies are integrated into DTx applications remains in the early stages.[1,3,4] For instance, rather than relying on AI-enabled predictions, the majority of DTx interventions involve software using generic fixed algorithms that do not change dynamically from patient to patient and do not consider unique personalized patient symptom data. In the case of VR instead, key challenges relate to technical hurdles (i.e. discomfort for users) and ethical issues (i.e. users' privacy due to the acquisition of users' behavioral biometrics data), that play a key role in hindering the adoption rates of VR in this field.[3,21]

Thus, the next section aims to advance our understanding of the state of the art of the different technological enablers of DTx by offering an overview of their characteristics, applicability, and respective challenges.

Enabling technologies and tools for DTx applications

In this section, we start by discussing the state of mHealth applications, as they are currently widely adopted for DTx.[4] Second, we provide insights on AI integrations into DTx products, since this might lead to a customized and more tailored therapy regimen, as suggested by Palanica et al., [1] Finally, we discuss VR-enabled DTx applications due to their expanding role in this field.[21]

Mobile applications: the US FDA defines a mobile application as a software application that can be run on a mobile platform, or a web-based software application that is tailored to a mobile device.[22,23] Some are standalone apps, while others require a connection to an external device, such as an inhaler or a wearable device. Here, the considered mHealth apps are used by individuals, typically on a mobile device such as a smartphone, smartwatch, or tablet, for therapeutic purposes.[23]

Mobile applications are indeed used for a variety of tasks such as providing feedback to reinforce positive behavioral change (e.g. physical activity, food intake,[24] medication adherence,[25] and substance consumption[26]), frequently adjust individually tailored programs, improve access to established therapies (e.g. CBT), and support ongoing connections with healthcare professionals through messaging features.[27] Moreover, as mHealth apps have greater flexibility, they become a more accessible, low-cost, and user-friendly alternative to traditional interventions.[8,28] For instance, mobile DTx platform Clickotine, helps smokers quit using a customized plan and scientifically based strategies to overcome cravings as well as social support and direct access to quit aids.[26,29]

Moreover, app-based DTx interventions are effective for several common mental health problems such as improving depressive symptoms, anxiety symptoms, stress levels, general psychiatric distress, and quality of life. Although mental health apps are not meant to replace professional clinical services, the present findings highlight their potential to serve as a cost-effective, easily accessible, and low-intensity intervention for the millions of people worldwide who cannot receive standard psychological treatment. There is also huge potential for real-world data generation since apps allow continuous real-time data collection on the patient's phone, leading to the personalization of the care process and to the reduction of bias in healthcare databases and algorithms.[28]

Artificial intelligence: AI could play a significant role in driving personalization and increasing engagement of DTx interventions. AI-enabled DTx promise to provide more personalized support to better address a patient's specific issues and to anticipate needs and challenges based on the individual's behavior throughout their treatment journey.

DTx relying on AI as a component of treatment can benefit from the "learning" feature typical of this technology that can help extract patterns from large datasets (e.g. data collected from a patient over time) and generate predictive models for the management and treatment of conditions, thus potentially increasing the effectiveness of digital interventions through a customized therapy regimen.[5,30] In fact, since AI systems can constantly collect data from the patient and his/her environment (e.g. engagement and biometric data), they can be programmed to change the delivery of treatment in response to outputs of algorithms,[1,30] and optimize data input to personalize outcomes. AI integration could further differentiate DTx from other forms of therapeutics, by enabling a more personalized form of healthcare that actively adapts to patients' individual clinical needs, goals, and lifestyles.[1] For instance, an AI-powered chatbot (i.e. software that utilizes natural language processing (NLP) to create an interface that emulates human discourse, and elements of human relationships) can be used to provide CBT, medication adherence reminders, or online exercise and diet programs.[1]

Table 1 presents some of the DTx applications that currently integrate AI. These product/company examples were selected from our DTx database.

While AI holds great promise for digital interventions, today AI-enabled DTx applications can be considered in the early phase due to a limited number of commercialized products and limited evidence from academic and clinical applications.[1,30] Additionally, privacy and ethical concerns related to patient data acquisition, processing, and governance, and cultural resistance to AI-based decision-making are some of the limitations that remain to be addressed.[41] For instance, considering chatbot-based interventions, the lack of empathy and professional human approach is reported as an undesirable feature by some users.[42]

One additional relevant drawback of AI systems is the need to create a representative, diverse dataset to build safe and efficient algorithms for AI-enabled DTx interventions. Indeed, the performance of healthcare algorithms is affected by social bias and other biases in health training datasets.[43,44] Methods to recognize and remove such

Table 1. Overview of various DTx products and their convergence with artificial intelligence.

DTx product/ Company	Target disease/ syndrome	Description	Related clinical evidence (dates, title)
WB001 / Woebot Health[31]	Postpartum depression	WB001 is an investigational 8-week digital therapy comprising a mobile patient application intended to deliver CBT and some elements of IPT to women who have recently given birth, in order to reduce the symptoms associated with Postpartum Depression. WB001 offers the patients dynamic and personalized features such as mood tracking and goal-oriented tailored conversations aiming to enable the automation of measurement-based care. WB001 was granted Breakthrough Device Designation by the FDA in 2021.	2020–2021: Postpartum Depression Pivotal Test: Randomized Clinical Trial of WB001 (Allocation: Randomized)[32]
Zemedy/Bold Health[33]	Irritable bowel syndrome	The Zemedy app consists of 8 modules focusing on psychoeducation, relaxation training, exercise, the cognitive model of stress management, applying CBT to IBS symptoms, reducing avoidance through exposure therapy, behavioral experiments, and information about diet. Users interact with a chatbot that presents the information and encourages specific plans, homework, and exercises. The treatment was fully automated, with no therapist involvement or communication.	2019–2020: Acceptability and Efficacy of the Zemedy App for Irritable Bowel Syndrome (Allocation: Randomized)[34] 2021-ongoing: Zemedy - Evaluation of Zemedy, a Cognitive Behavioral Therapy-based Digital Therapeutic Application for the Treatment of Irritable Bowel Syndrome (Allocation: Randomized)[35] 2021-ongoing: Acceptability and Efficacy of Zemedy App Versus Education and Relaxation Training App for IBS (Allocation: Randomized)[36]
Sleepio/Big Health[37,38]	Insomnia	The Sleepio app leverages an AI algorithm to offer tailored digital CBT for insomnia. The Sleepio app can be linked to a compatible wearable fitness tracker to monitor sleep. The program is structured around a sleep test, weekly interactive sessions and regular sleep diary entries. In a clinical trial, Sleepio helped 76% of people achieve clinical improvement in insomnia. Additionally, a health economic evaluation of Sleepio shows that the cohort of Sleepio users had 28% lower healthcare costs.	Several RCTs explore the efficacy of Sleepio. Some of them are: 2019: Effect of Digital Cognitive Behavioral Therapy for Insomnia on Health, Psychological Well-being, and Sleep-Related Quality of Life: A Randomized Clinical Trial[39] 2022-ongoing: Improving Sleep and Learning in Rehabilitation After Stroke, Part 2 (Allocation: Randomized)[40]

CBT: cognitive behavioral therapy; IPT: interpersonal psychotherapy; IBS: irritable bowel syndrome.

biases are paramount to ensuring the delivery of equitable healthcare and promoting transparency in AI-enabled DTx. To address this issue, developers, users, and regulators need to work together to leverage large and diverse datasets to improve accuracy while balancing privacy and regulatory requirements. Critically, clinicians should carefully limit overreliance on these systems in decision-making, understanding the limitations of AI-enabled DTx decision model interpretability. Special consideration is even more needed for those AI applications targeted directly to patients, which is mostly the case for DTx interventions, where patients may not be in the appropriate position to judge if the suggested action is reasonable.[43]

Virtual reality: VR might constitute an effective tool for therapeutics, making the user experience more engaging and accessible by gamifying interventions and providing virtual care at locations ranging from care centers to patients' homes.[19] The increasing use of computing power and connectivity capabilities in VR headsets and the improved ergonomics are becoming important features for increasing the integration of VR technology into DTx interventions.[45] VR-based DTx address therapeutics fields including mental health, anxiety disorders,[46] ADHD,[47] eating and weight disorders,[48] pain management,[49] cancer care,[50,51] and many others.[52] There are several DTx products and studies using VR technologies. Specific relevant

examples and related details are presented in Table 2. For instance, Luminopia received FDA de novo premarket approval for Luminopia One as a prescription therapy to improve vision in children with amblyopia (lazy eye), the leading cause of vision loss in children. Luminopia One delivers prescription-only treatment for patients, in the form of TV shows and movies viewed through a VR headset for an hour each day.[53] Similarly, EaseVRx by the company AppliedVR, received FDA approval in 2021 for a prescription-use immersive VR system, that guides patients through games, lessons, and exercises that are backed by CBT and other practices to help ease their chronic pain.[54]

In the realm of VR technical possibilities, potential further development with positive repercussions on DTx could come from the integration of VR with AI, that might further increase the "*personalization of DTx*" and could become a tool for improving evidence-based psychological treatments.[21] In fact, while VR allows physiological and behavioral data collection (e.g. biological responses to therapeutic interventions that are directly connected to brain functioning), AI optimizes the individual treatment strategy by applying ML techniques to these data.[21]

This field is new and rapidly evolving, and as such its risks and benefits are continuing to be studied. Nearly every study that has been conducted on these technologies points out that more research is required to answer key questions, including effectiveness and safety.[21,52]

Table 2. Overview of various DTx products and their convergence with virtual reality.

DTx product/Company	Target disease/ syndrome	Description	Related clinical evidence (dates, title)
Luminopia / One Luminopia[53,55]	The treatment of amblyopia	Luminopia One is a VR-based DTx that modifies the selected videos in real-time within a VR headset to rebalance input between the eyes and encourages the brain to combine the images from both eyes. The findings from a randomized controlled trial support the value of this solution in clinical practice as an effective treatment.	2017–2019: Luminopia One Pilot Study[56] 2019–2020: Luminopia One Amblyopia Vision Improvement Study (Allocation: Randomized) [55]
RelieVRx / AppliedVR[57]	Chronic pain	RelieVRx (formerly EaseVRx) is an at-home VR-based pain treatment indicated as an adjunctive treatment for chronic lower back pain. The study shows that EaseVRx had high user satisfaction and clinically meaningful symptom reduction for average pain intensity and pain-related interference with activity, mood, and stress.	2021–2023: Safety and Effectiveness of Virtual Reality Utilizing RelieVRx for Total Knee Arthroplasty (TKA) for the Reduction of Acute Postoperative Pain and Opioid Use (Allocation: Randomized)[58] 2023-ongoing: Virtual Reality Treatment in a Methadone Maintenance Treatment Program for Chronic Pain and Opioid Use Disorder (Allocation: Randomized)[59]
Journal of Pediatric Oncology Nursing, 2021 (Journal)[60]	Pain management in oncology	Needle procedures are one of the most distressing practices for pediatric oncology patients. VR is a distraction method that offers an extremely realistic and interactive virtual environment and helps reduce needle-related pain and distress. The study shows that for both the children and the parents, VR becomes effective in reducing pain during venous port access in pediatric oncology patients. Further research is required to assess the use of VR together with other nonpharmacological or/and pharmacological methods so that VR-based pain management could give more favorable results.	2020: Effects of Virtual Reality on Pain During Venous Port Access in Pediatric Oncology Patients: A Randomized Controlled Study

The role of regulation and the key challenges of DTx

In the evolving landscape of DTx, certain countries are making efforts to ease the integration of these medical solutions into the healthcare system, despite the regulatory challenges akin to those faced by traditional medical devices. Notably, the United States and Germany have emerged as frontrunners in this regard. In the United States, the FDA is actively working to simplify the regulatory process for Software as a Medical Device (SaMD).[61] This initiative might accelerate the adoption of DTx by streamlining the approval process for these technologies. At the same time, Germany has taken significant steps to incorporate digital health applications (DiGAs) into its healthcare system.[62] German doctors are now authorized to prescribe DiGAs to patients, who can then have these prescriptions covered by health insurance. This approach not only legitimizes the use of DTx but also enhances their accessibility to a broader patient population.

In this scenario, DTA is one of the global non-profit associations leading the discussion and development of harmonized pathways for the recognition and scalability of DTx at the local, national, and regional levels.

Nevertheless, despite these efforts, there is not a global regulatory framework for DTx. This absence may be attributed, in part, to the inherently dynamic nature of DTx themselves. As outlined in the previous section, DTx are exploiting new emerging technologies, undergoing constant evolution to leverage the latest technological advancements. This perpetual state of evolution presents a challenge in establishing a universally applicable regulation for DTx. Furthermore, distinguishing DTx from pharmaceuticals and traditional medical devices is their capacity for frequent updates and enhancements. This characteristic introduces an additional layer of complexity for regulatory bodies. The challenge lies in developing a regulatory mechanism that can effectively manage and monitor the rapid evolution inherent to DTx, ensuring both their efficacy and safety over time.[5]

Indeed, it appears that the regulatory landscape is complex, evolving quickly, and different in each country.[17] This section aims to provide a comprehensive examination of this issue, beginning with an overview of the current regulatory landscape for DTx in the EU and the US. Subsequently, it delves into the challenges associated with the socio-ethical implications of DTx, highlighting the intricate balance between innovation and ethical considerations in the deployment of these technologies.

(a) The state of regulation in European Union (EU) and United States (US)

Regulatory framework in the EU

DTx are covered by EU regulation 2017/745 on medical devices,[63] which came into force in May 2021. The EU Medical Device Regulation contains no specific provisions for DTx and the approach to be taken by notified bodies concerning regulations applicable to DTx.[64] Although in some European countries, several procedures have been set up for the marketing authorization and reimbursement of DTx, the European regulatory system concerning DTx remains uncoordinated, and specific regulations aimed at evaluating DTx tools and ensuring the safety of the devices are lacking.[65,66]

Since the development and delivery features of DTx are similar to those of conventional drugs, evidence of efficacy and safety must be provided before they can be authorized for marketing. The evaluation of the efficacy and safety of DTx should be based on high-quality controlled clinical trials carried out according to the standards required by regulatory agencies.[65] Indeed, the lack of specific regulations to guarantee the safety and quality of these devices is a further obstacle to the development of DTx.[17,64] In addition, considering that Europe is neither a single unified market nor does it have mutual recognition of certification, a parliamentary question titled "*Single Market for Digital Therapeutics*" was raised on 7 November 2022. This action highlights the pressing need for a clear EU model for DiGAs reaching patients, as national models are causing fragmentation in the EU single market.[66]

Given that Germany has taken the lead on introducing many DTx products to the market since 2020 (enabling fast-track authorization under controlled conditions), its model could be considered a valid, useful template for other European countries to enable innovation and adoption of DTx.[67] For this reason, the next session is dedicated to the in-depth analysis of the regulation in Germany.

Regulatory framework in the EU–the case of Germany

In recent years, Germany has established itself as a pioneer in digital health innovation in Europe,[68] with 73 million German citizens covered by public health and DTx apps approved for reimbursement. The country that paved the way for DTx has inspired other European countries—that is, Belgium and France.[67]

At the end of 2019, Germany implemented the Digital Healthcare Act (Digitales Versorgungsgesetz, DVG) which established a specific pathway for the reimbursement of digital health offerings. This act aimed to enhance transparency in the approval process for manufacturers, physicians, and patients in Germany. Under the fast-track process, DiGAs can be prescribed by doctors and reimbursed by health insurance companies. In order to gain access to the market, developers must register their CE-marked device (class I or IIA) at the Federal Institute for Drugs and Medical Devices (BfArM), and complete the compliance process of a DiGA with general

requirements (e.g. app security, quality, functionality, data security, and data protection) and its positive healthcare effects (i.e. medical benefit or improvements of care structure and processes). To gain a permanent listing in the DiGA directory (DiGAV), the developer must submit such evidence and undergo review. As of November 2022, the approved DiGAs in Germany cover a wide range of medical fields including diabetes, obesity, depression, anxiety, insomnia, and back pain therapy.[62]

Amid this environment in Germany, the prescription rate remained low.[69,70] A study performed among rheumatologists in 2022 reports that only 7% have already prescribed a DiGA and 46% planned to do so.[69] This is aligned with another research held in 2021 among members of the German Respiratory Society, where 47.2% HCPs had prescribed or planned to prescribe DIGA.[70] This further highlights that, even in a positive environment like Germany's, the adoption of DTx remains very low.

Regulatory framework in the US

Currently, the US is the driving force in the world for the development and commercialization of DTx.[64] The FDA has issued many temporary policies to support digital health innovation during the Covid-19 pandemic, particularly guidance documents to expand the use of DTx, especially with regard to mental disorders like depression[71] and chronic ailments like diabetes. Today, FDA is leading in formally approving DTx, including the most recent and innovative interventions.

From a regulatory point of view, DTx products in the US are considered within the SaMD category.[61] Based on the DTx's intended use and level of risk, each product is subject to varying degrees of oversight, ranging from full 510(k) clearance by the FDA's Center for Devices and Radiological Health (CDRH) division to enforcement discretion.[2,72] Beyond direct approval processes, the FDA has also recently established the Digital Health Center of Excellence (DHCoE) in September 2020 with the intent to speed the innovation of safe and effective digital technologies.[73] DHCoE acts as a central authority intended to manage and speed digital innovation (including SaMD, wearables, mobile health devices, AI, and ML that may be built into SaMD and medical applications).

While these incentives are helpful, the FDA and other regulatory bodies still need to adapt to the speed of technology and establish clear parameters for regulation and enforcement.

(b) Socio-ethical issues during the design and implementation stage of DTx.

The utilization of DTx is linked to several socio-ethical barriers among stakeholders, encompassing factors such as infrastructure limitations, health inequalities and bias, and liability issues. This section outlines the key socio-ethical issues that arise during the design and implementation stages of DTx.[74]

Data protection issues, patient profiling, and cybersecurity concerns.[75] The current DTx applications developed in the market remain vulnerable to data breaches and cyberattacks. A vast amount of personal data is collected directly from the patient and processed in a complex digital ecosystem. In most cases, accurate health and/or behavioral profile of the person are created, and this might entail risks of being constantly observed or the possibility of repurposing patients' profiles. Moreover, other entities such as insurance companies, device manufacturers, or cloud storage service providers and managers may necessitate access to patient data. The use of such data can lead to complex issues related to confidentiality.[76] The large quantity of sensitive data generated by these technologies and no specific DTx regulations in terms of data protection and cybersecurity call institutions and regulatory bodies to produce governance structures for DTx products.[64]

Health inequalities, digital literacy, and digital divide. Despite the anticipation that health information technology could substantially tackle inequitable health outcomes influenced by demographic and sociocultural determinants (e.g. age, gender, cultural background, cognitive abilities, digital literacy, and digital divide) the persistence of poor health outcomes linked to these determinants remains. The implementation of new technologies has not significantly alleviated these issues and, in some cases, may have even exacerbated them.[76]

A significant concern is the potential challenges posed by the digital divide (limited access to technology) and digital literacy (lack of technological literacy). These factors could have negative implications for the adoption of DTx, adherence, and diffusion. Existing literature underscores that digital literacy skills in the healthcare context are associated with various health behaviors, including maintaining a healthy diet, engaging in exercise, and managing sleep. Furthermore, associations have been observed between digital health literacy and factors such as the presence of chronic illness, perceived self-management skills, and an enhanced self-perceived understanding of health status, symptoms, and optional treatments. Therefore, fostering digital literacy and addressing concerns related to the digital divide can positively impact perceptions of DTx, subsequently increasing the intention to use DTx.[77]

Fair and liable AI-based DTx. As discussed in section "Enabling technologies and tools for DTx applications," some DTx tools incorporate AI algorithms. Inequalities within healthcare-related datasets can impact the training datasets of AI algorithms, potentially intensifying existing biases and leading to discrimination issues. This can be further compounded by the underrepresentation of certain groups in the development phase, ultimately resulting in a suboptimal DTx intervention system.

Furthermore, this situation raises liability concerns, posing the question of who ultimately holds responsibility for patients' health: the AI software or the prescribing physician of the DTx system. This adds complexity to the issue of accountability.[76]

The trade-off between increased patient autonomy and decreased direct interaction with the physician. On the one hand, when utilized appropriately, these technologies can facilitate safe and effective care delivery by empowering patients to manage their own health and encouraging the efficient sharing of relevant health information.[74] On the other hand, there is a potential risk, to some extent, that it may compromise the patient–physician relationship. Although the integration of DTx enables a continuous dialogue between clinicians and their patients, there is a risk that excessive dependence on technology may reduce the necessity for a direct relationship with the physician.[76]

(c) Other challenges

Given the wide content and applications of DTx, it is unlikely that there will be a one-size-fits-all approach for DTx regulations and ethics. Building on the previously discussed findings, our research has identified challenges beyond regulatory and ethics, including (1) the design of the clinical trials and evidence generation methods in DTx seeking regulatory approval[6,78]; (2) the limited evidence and a lack of understanding of efficacy related to the digital mode of delivery[79,80]; (3) adherence/compliance with DTx products and engagement support by HCPs.[78,79]

Design of clinical trials and evidence-generation methods in DTx seeking regulatory approval. Randomized controlled trials (RCTs) remain a key evidence-generation step for most DTx.[6,78] However, DTx differ from the ones for drugs and medical devices. Indeed, DTx present peculiar characteristics that raise specific needs to be addressed during study design to assess the risk-benefit profile: choice of control and metrics for outcome measurement in relation to efficacy and safety, must often be customized on a case-by-case basis.[81] For instance, digital placebo mechanisms and impacts remain to be understood for effective DTx clinical trials (e.g. beliefs about technology, and the feeling of being connected to coaches or a therapist through using a DTx app).[78] To date, precise recommendations in the regulations considering the required characteristics of clinical trials to support DTx certification in Europe remain absent.[81] A critical question is also raised due to AI technology integration into DTx as if the regulator should limit its authorization to market only the version of the algorithm that was submitted or allow the integration of an algorithm that can learn and adapt to new conditions.[82]

The limited evidence and a lack of understanding of efficacy (measures and measurement processes) related to the digital mode of delivery. The incremental nature of the technological development of DTx makes RCTs in some cases unsuitable to demonstrate efficacy. Additionally, the sample bias risk in clinical studies remains and the clinical findings may not be generalized to patient groups other than those enrolled in the specific clinical study (e.g. based on ethnicity, socioeconomic status, and level of education).[80] Finally, how DTx will be evaluated against conventional therapeutics through comparative effectiveness studies also has yet to be explored.[5]

Adherence/compliance with DTx products and engagement support by HCPs. While retention is one of the most significant issues for any eHealth intervention (e.g. health and wellness apps), it becomes crucial for DTx products. DTx require the patient's and/or caregiver's active involvement in the care pathway, gathering clinical evidence and directly affecting the treatment results.[64,78,79] The literature highlights HCPs' training and level of confidence with technology as significant factors in increasing patient adherence and effectiveness of DTx products.[68] However, currently, most healthcare stakeholders do not fully leverage the role of HCPs in promoting both access and patient adherence to DTx.[68] The influence of HCP organizations, such as medical associations, professional societies, or doctor networks, was considered to have a potentially positive impact on this issue, given their extensive reach, trust among HCPs, and influence on them.[68]

Other key solutions are to design DTx tools to increase adherence through both product features and to embed DTx treatment in the patient's care pathway. Key considerations on the patient's side include optimizing for user-friendliness, incorporating tailoring and personalization, integrating gamification elements, utilizing reminders, and ensuring patients comprehend the value of DTx for their health. Lastly, it is crucial to establish convenient methods aligned with existing practice operations and workflows to enable HCPs to monitor the usage of DTx.

Due to the relatively recent emergence of DTx, there has been limited research into approaches for introducing technologically advanced DTx solutions to the market, staying aligned with regulatory bodies for approvals and reimbursements, and promoting the adoption and adherence of DTx. Moreover, considering the therapeutic nature of these digital interventions, there is a need for additional research on the ethical implications specific to this field, beyond the considerations for general digital health products.

Figure 3 provides an overview of the main identified challenges.

Discussion

The advent of DTx has promised to move healthcare to another and more contemporaneous level. DTx offer

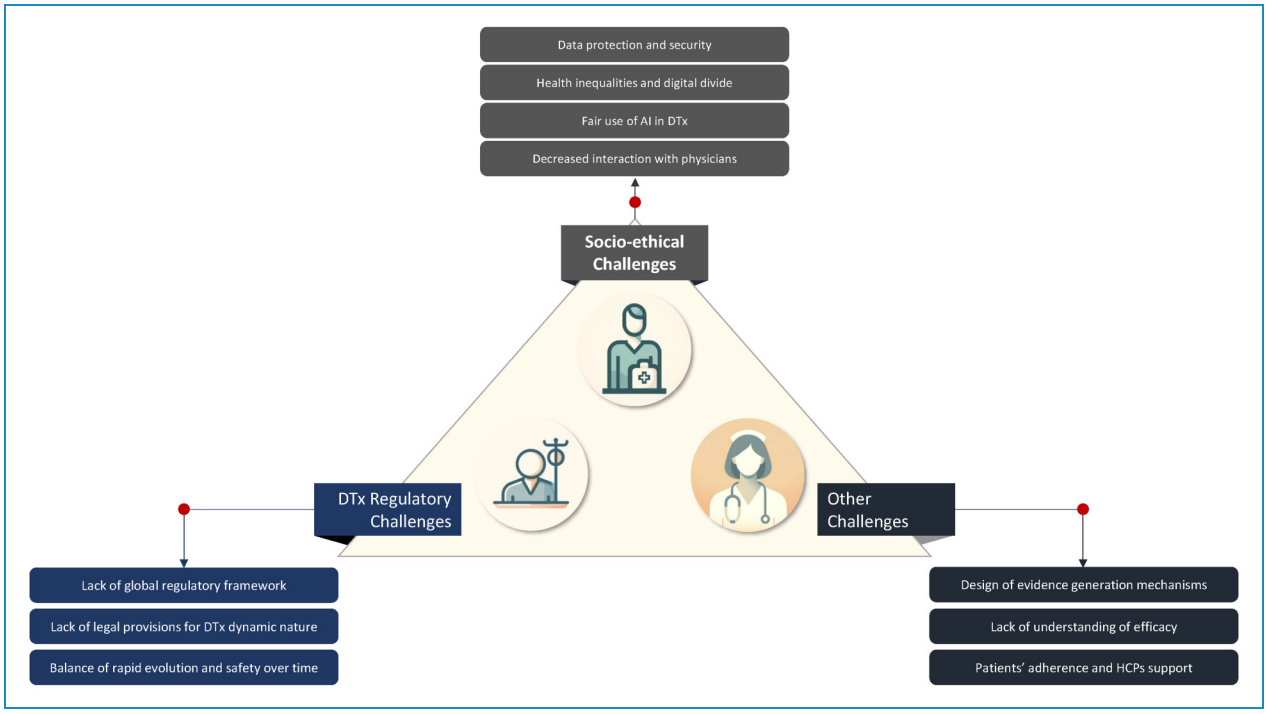

Figure 3. Overview of the main challenges of DTx clustered in regulatory, socio-ethical, and other challenges.

potential solutions for treatment gaps, enhancing patient engagement, and are a key tool for personalizing medicine to an unprecedented level. However, the path to integrate these digital solutions into healthcare systems is laden with challenges that need to be addressed, including uncoordinated, non-specific and evolving regulations, lack of a universally accepted definition, inadequate ad-hoc evidence of clinical efficacy, and data protection concerns. Until recently, research on the domain of DTx has focused on several relevant aspects that need to be addressed to foster the diffusion of this novel form of therapeutics. Studies have attempted to conceptualize and define DTx,[1,2,5,6] provide early evidence of the effectiveness of DTx treatments in specific domains, thus investigating on their potential to evolve treatment models,[5,7–9] and deep dived into the technological enablers of these digital therapies.[4,5,21] Moreover, literature has explored various types of challenges surrounding the diffusion of DTx. Among these, regulatory uncertainty, socio-ethical concerns, and several concerns related to the effectiveness and acceptance of DTx by patients and HPCs. Notwithstanding the several streams of research that are focusing on DTx from these separate perspectives, evidence from this review paper shows that such concepts and challenges need to be examined and addressed with a comprehensive approach. Therefore, our review paper collects and organizes previous research with specific vertical focuses and aims to introduce managerial lenses to support the diffusion on DTx.

In particular this paper provides three main contributions. First, we provide a definition of DTx based on a synthesis of diverse definitions. Second, we offer an extensive discussion of new emerging technologies and their integration in this field. Third, we present a comprehensive overview of the challenges for DTx adoption. Table 3 provides an overview of the three main findings, their descriptions, and the contributions to the literature compared to the existing discourse on this topic.

First of all, one of the fundamental gaps in the discourse on DTx is the lack of a universally accepted definition. This is important not just from an academic standpoint, but also as a crucial aspect for regulating, evaluating, and reimbursing these products. Indeed, the DTx nature is not so obvious: from a functional perspective, they are in many instances similar to pharmaceuticals (with the active ingredient being a digital solution instead of a chemical/biotechnological entity) but from a technological perspective, they are generally embodied into medical devices. As a consequence, the ambivalent nature of DTx is not fully understood using the traditional categories of drugs and medical devices, leading to a heterogeneous perception of what they are. This lack of consensus can lead to confusion among stakeholders, including patients, HCPs, regulators, and payers. It is crucial that stakeholders, led by international health bodies, come together to establish a shared understanding of what constitutes DTx, which should reflect the dynamic nature of this emerging field and cover all aspects from intended use to functionality and software requirements.

Second, most of the technological discourse around DTx focuses on mobile apps that enable new DTx. While this

Table 3. Overview of findings and contribution.

Finding	Finding–overview	Contribution
Definition of DTX	Defining DTx and distinguishing it from other digitally enabled medical applications.	Previous literature defined and distinguished DTx from related fields, but lacked comprehensive discussion. This review fills the gap by presenting diverse definitions and discussing similarities and differences with other digital health fields.
Technologic enablers of DTx	Summarizing the DTx literature on enabling technologies (e.g. mobile apps, AI, VR) and presenting relevant clinical evidence.	Most DTx interventions used basic software in mobile apps, limiting exploration of advanced technologies. This review initiates discussion on integrating advanced technologies like AI and VR into DTx from both technological and ethical perspectives.
Challenges for DTx adoption	Examining regulatory, ethical, and other challenges hindering market adoption.	Previous literature addressed various challenges but lacked a comprehensive approach. This review provides a comprehensive overview of challenges to facilitate informed discussions on adopting DTx solutions.

aspect remains crucial, integrating advanced technologies is essential for developing new features. For instance, this paper identifies the expanding role of AI in DTx products and the use of VR to deliver DTx. These technologies offer unique opportunities but also complicate the adoption process of DTx. Indeed, the adoption of AI and VR introduces new regulatory and socio-ethical issues. In particular, AI-enabled DTx pose a challenge for regulatory bodies, which must determine how to regulate algorithms that primarily rely on learning from data and adaptation. While their application is currently limited, tools like general-purpose large language models (LLMs), medical AI models (such as Med-Gemini), and generative AI systems (GenAI) are attracting increasing attention in healthcare.[83,84] Since ChatGPT's introduction in late 2022, GenAI has sparked both great enthusiasm and serious concerns.[85] To date, GenAI applications are mainly being evaluated for screening and diagnostics, such as predicting disease outcomes and improving diagnostic accuracy. GenAI also shows potential in care delivery processes and analyzing data for personalized medicine. Interest for the applicability of LLMs and GenAI is increasing also in the DTx field, but in general application remains limited and evidence of its use in health systems is lacking. Future research is expected to explore AI long-term impact, patient-centered outcomes, and scalability, as well as its impact on the treatment decisions and delivery.[86] As a result, discussions on regulating this field are expected to intensify, together with reflections on AI integration in DTx. Regarding VR, it is an essential technology to monitor, especially with the emergence of the Metaverse. While VR has not yet had a significant impact, it has the potential to be widely adopted in the coming years. This adoption could profoundly influence the field of DTx, creating new opportunities for innovation and patient care.

Third, this review identify a broad spectrum of challenges for DTx adoption in terms of regulatory, socio-ethical, the design of evidence-generation mechanisms, lack of understanding of efficacy, and patients' adherence and HCPs support. Primarily, regulatory issues pose significant challenges to the development and adoption of DTx. The regulatory landscape for DTx is currently fragmented and evolving. In the EU, for instance, there is a lack of specific provisions for DTx, leading to an uncoordinated regulatory system. The closest regulation is the one on medical devices, but DTx are not explicitly mentioned, and this has slowed down most Member States' adoption of ad-hoc regulatory pathways for DTx. Contrastingly, the US FDA has been more proactive, issuing guidance and even establishing the DHCoE to promote digital health innovation. Germany, too, has established a pioneering model for DTx regulation and reimbursement, which could serve as a blueprint for other countries. Nonetheless, regulatory harmonization across jurisdictions is required to facilitate the global expansion of DTx and ensure that patients worldwide can benefit from these innovative therapies. Moreover, the utilization of DTx is linked to several socio-ethical barriers among stakeholders, encompassing factors such as infrastructure limitations, health inequalities and bias, and liability issues. One of the significant concerns is that efficient DTx implementation fundamentally requires adequate health literacy and digital competency, such as the ability to use digital devices and understand information. Germany offers a relevant example. Despite establishing a pioneering model for DTx regulation and reimbursement, the prescription rate remains low. One possible reason is that HCPs and patients are not yet ready for this paradigm shift, in particular, due to patients having low health literacy and low confidence in using digital information for health decisions.[87,88] Furthermore, the sensitive nature of health

data collected and processed by DTx raises significant data protection and cybersecurity concerns. The potential for data breaches and cyberattacks necessitates robust data protection regulations and cybersecurity measures specifically tailored for DTx. Lastly, the absence of robust clinical evidence demonstrating the efficacy and safety of DTx is a further impediment to their adoption. The design of clinical trials for DTx needs to be tailored to their unique characteristics, with the choice of control and metrics for outcome measurement often needing to be customized on a case-by-case basis.

Overcoming these challenges will require a concerted effort from all stakeholders. For example, international health bodies could lead the charge in defining DTx and coordinating regulatory approaches, while developers could work closely with regulators to design suitable clinical trials and robust data protection measures. Meanwhile, HCPs could play a crucial role in promoting patient adherence to DTx, thus generating the real-world evidence needed to demonstrate their efficacy.

Limitations and future research

While this paper offers contributions to both academic research and practical applications, it is important to recognize its limitations. These limitations not only inform the evaluation of the findings presented in the paper but also pave the way for future research directions. The main limitations are divided into two groups: methodological limitations and uncovered areas of analysis.

First, from a methodological standpoint, as presented in section "Methods," this paper is based on the analysis of 74 articles from journals and clinical trial reports, 13 sources from global authority releases, including DTA publications, and 1 DTx company report to support our findings. The selection process involved identifying relevant keywords from previous studies,[5,10] which guided our research. While our analysis distinguishes itself from past research, we invite future studies to extend this review by incorporating new keywords that may reveal additional insights. Moreover, in the analysis of this paper, we adopted a manual review process. However, future researchers could implement more advanced clustering techniques, such as those based on NLP, to enhance the analysis and eventually identify additional findings and contributions.

Second, the paper identifies significant challenges for DTx, notably regulatory hurdles and the lack of robust clinical evidence. These challenges are particularly critical as they impact the adoption and efficacy of DTx. By highlighting these issues, this paper contributes to the academic discourse and opens new research avenues. Future research should delve deeper into these challenges, focusing on strategies to overcome regulatory barriers and enhance clinical evidence. Addressing these gaps will be crucial for advancing the field and ensuring the successful implementation of DTx solutions. Finally, this paper does not address the economic impact, whether positive or negative, of adopting DTx. We acknowledge the importance of this aspect and believe it is a crucial component that warrants detailed examination. Future research should investigate the economic implications of DTx adoption, considering factors such as cost-effectiveness, potential healthcare savings, and economic barriers to implementation. Understanding the economic impact will provide a more comprehensive view of DTx and support informed decision-making in healthcare policies and practices.

Conclusion

While there are great examples of technologically advanced DTx solutions emerging in the market, the road to widespread adoption is still paved with obstacles. To synthesize our findings and bridge the gap between DTx suppliers and patients, we propose five recommendations: First, we advocate for promoting a convergence of DTx definitions. International health bodies should lead the process of establishing a universally accepted definition that encompasses all aspects of these novel solutions, clarifying their hybrid nature. Second, there is a need to harmonize regulatory approaches. Regulatory bodies across different jurisdictions should collaborate to standardize regulations applicable to DTx, facilitating their global expansion and ensuring worldwide patient access. Corresponding reimbursement rules and models should also be considered. Third, we suggest designing tailored clinical trials. DTx developers should collaborate closely with regulators to develop customized methods for clinical trials that consider the unique characteristics of DTx. This entails creating customized controls and metrics for outcome measurement to accurately assess efficacy and safety, consistent with future DTx regulations. Fourthly, there is a crucial need to establish ad-hoc data protection and cybersecurity measures. Given the sensitive nature of health data collected and processed by DTx, developers must prioritize robust data protection and cybersecurity safeguards. Regulatory bodies should provide clear guidelines and requirements in this area. Finally, promoting HCPs engagement and patient adoption and adherence is essential. HCPs should receive training and encouragement to promote access to DTx and encourage patient adoption and adherence. Their active involvement can bolster patient confidence in DTx and generate real-world evidence necessary to demonstrate efficacy.

List of Abbreviations

AI	Artificial intelligence
ADHD	Attention-deficit hyperactivity disorder
BfArM	Federal Institute for Drugs and Medical Devices
CBT	Cognitive behavioral therapy
CDRH	Center for Devices and Radiological Health

CE	Conformité Européenne
DHCoE	Digital Health Center of Excellence
DiGAs	Digital health applications
DiGAV	DiGA Directory
DTA	Digital Therapeutics Alliance
DTx	Digital therapeutics
DVG	Digital Healthcare Act
EU	European Union
FDA	US Food and Drug Administration
GenAI	Generative AI
HCPs	Healthcare providers
IBS	Irritable bowel syndrome
IPT	Interpersonal psychotherapy
LLMs	Large language models
NLP	Natural language processing
RCTs	Randomized controlled trials
SaMD	Software as a Medical Device
TKA	Total knee arthroplasty
US	United States
VR	Virtual reality.

Contributorship: Paper conceptualization and review: P.A., A.G. Literature review: I.P. Manuscript writing: P.A., I.P., L.M.D.R., L.D., S.M. All authors have read and agreed to the published version of the manuscript.

Declaration of conflicting interests: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was funded through SDA Bocconi's LIFT Lab, which is supported by AB MEDICA SPA, BRACCO IMAGING SPA, FOND. E.A. FIERA INTERN. MILANO, FONDAZIONE CARIPLO, FONDAZIONE ENPAM, INTESA SANPAOLO FORMAZIONE SPA, INTESA SANPAOLO INNOVATION CENTER SPA and MEDTRONIC ITALIA SPA. This research was also co-funded by a SDA Bocconi internal research grant focused on Digital Therapeutics.

ORCID iD: Irem Polat https://orcid.org/0000-0001-8733-2953

References

1. Palanica A, Docktor MJ, Lieberman M, et al. The need for artificial intelligence in digital therapeutics. *Digit Biomarkers* 2020; 4: 21–25.
2. Digital Therapeutics Alliance. Digital therapeutics alliance, https://dtxalliance.org/ (2023, accessed 15 April 2023)
3. Abbadessa G, Brigo F, Clerico M, et al. Digital therapeutics in neurology. *J Neurol* 2022; 269: 1209–1224.
4. Santoro E, Boscherini L and Caiani EG. Digital therapeutics: a systematic review of clinical trials characteristics. *Eur Heart J* 2021; 42: ehab724 . 3115.
5. Patel NA and Butte AJ. Characteristics and challenges of the clinical pipeline of digital therapeutics. *NPJ Digit Med* 2020; 3: 1–5.
6. Huh KY, Oh J, Lee S, et al. Clinical evaluation of digital therapeutics: present and future. *Healthc Inform Res* 2022; 28: 188–197.
7. Kollins SH, DeLoss DJ, Cañadas E, et al. A novel digital intervention for actively reducing severity of paediatric ADHD (STARS-ADHD): a randomised controlled trial. *Lancet Digit Health* 2020; 2: e168–e178.
8. Ellis TD and Earhart GM. Digital therapeutics in Parkinson's disease: practical applications and future potential. *J Parkinsons Dis* 2021; 11: S95–S101.
9. Iivanainen S, Alanko T, Vihinen P, et al. Follow-up of cancer patients receiving anti-PD-(L) 1 therapy using an electronic patient-reported outcomes tool (KISS): prospective feasibility cohort study. *JMIR Format Res* 2020; 4: e17898.
10. Sverdlov O, Van Dam J, Hannesdottir K, et al. Digital therapeutics: an integral component of digital innovation in drug development. *Clin Pharmacol Ther* 2018; 104: 72–80.
11. Dang A, Arora D and Rane P. Role of digital therapeutics and the changing future of healthcare. *J Family Med Prim Care* 2020; 9: 2207.
12. World Health Organization. mHealth programmes are sponsored by government. https://www.who.int/data/gho/indicator-metadata-registry/imr-details/4774 (nd, accessed 20 August 2023)
13. Fürstenau D, Gersch M and Schreiter S. Digital therapeutics (DTx). *Bus Inf Syst Eng* 2023; 65: 349–360.
14. Wang C, Lee C and Shin H. Digital therapeutics from bench to bedside. *NPJ Digit Med* 2023; 6: 38.
15. Yan K, Balijepalli C and Druyts E. The impact of digital therapeutics on current health technology assessment frameworks. *Front Digit Health* 2021; 3: 667016.
16. op den Akker H, Cabrita M and Pnevmatikakis A. Digital therapeutics: virtual coaching powered by artificial intelligence on real-world data. *Front Comput Sci* 2021; 3: 750428.
17. Rassi-Cruz M, Valente F and Caniza MV. Digital therapeutics and the need for regulation: how to develop products that are innovative, patient-centric and safe. *Diabetol Metab Syndr* 2022; 14: 48.
18. Auster-Gussman LA, Lockwood KG, Graham SA, et al. Reach of a fully digital diabetes prevention program in health professional shortage areas. *Popul Health Manag* 2022; 25: 441–448.
19. Kario K, Harada N and Okura A. The first software as medical device of evidence-based hypertension digital therapeutics for clinical practice. *Hypertens Res* 2022; 45: 1899–1905.
20. Wang Z, Xiong H, Zhang J, et al. From personalized medicine to population health: a survey of mHealth sensing techniques. *IEEE Internet Things J* 2022; 9: 15413–15434.
21. Riva G, Wiederhold BK, Di Lernia D, et al. Virtual reality meets artificial intelligence: the emergence of advanced digital therapeutics and digital biomarkers. *Ann Rev CyberTher Telemed* 2019; 17: 3–7.
22. U.S. Food and Drug Administration. Policy for device software functions and mobile medical applications. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-device-software-functions-and-mobile-medical-applications (2022, accessed 1 February 2023)
23. Gordon WJ, Landman A, Zhang H, et al. Beyond validation: getting health apps into clinical practice. *NPJ Digit Med* 2020; 3: 14.
24. Moravcová K, Karbanová M, Bretschneider MP, et al. Comparing digital therapeutic intervention with an intensive

obesity management program: randomized controlled trial. *Nutrients* 2022; 14: 2005.
25. Park JY, Li J, Howren A, et al. Mobile phone apps targeting medication adherence: quality assessment and content analysis of user reviews. *JMIR Mhealth Uhealth* 2019; 7: e11919.
26. Tong F, Lederman R, D'Alfonso S, et al. Digital therapeutic alliance with fully automated mental health smartphone apps: a narrative review. *Front Psychiatry* 2022; 13: 819623.
27. Rowland SP, Fitzgerald JE, Holme T, et al. What is the clinical value of mHealth for patients? *NPJ Digit Med* 2020; 3: 4.
28. Linardon J, Cuijpers P, Carlbring P, et al. The efficacy of app-supported smartphone interventions for mental health problems: a meta-analysis of randomized controlled trials. *World Psychiatry* 2019; 18: 325–336.
29. ClinicalTrials.gov. Clinical learning study for a mobile smoking cessation program. https://clinicaltrials.gov/ct2/show/NCT04857515 (2021, accessed 20 February 2023).
30. Guthrie NL, Berman MA, Edwards KL, et al. Achieving rapid blood pressure control with digital therapeutics: retrospective cohort and machine learning study. *JMIR Cardio* 2019; 3: e13030.
31. Darcy A, Beaudette A, Chiauzzi E, et al. Anatomy of a Woebot®(WB001): agent guided CBT for women with postpartum depression. *Expert Rev Med Devices* 2022; 19: 287–301.
32. ClinicalTrials.gov. Pivotal Test: WB001. https://classic.clinicaltrials.gov/ct2/show/NCT04576754 (2022, accessed 20 August 2023)
33. Hunt M, Miguez S, Dukas B, et al. Efficacy of Zemedy, a mobile digital therapeutic for the self-management of irritable bowel syndrome: crossover randomized controlled trial. *JMIR Mhealth Uhealth* 2021; 9: e26152.
34. ClinicalTrials.gov. Acceptability and Efficacy of the Zemedy App for Irritable Bowel Syndrome. https://classic.clinicaltrials.gov/ct2/show/study/NCT04170686?term=zemedy&draw=2&rank=3 (2021, accessed 20 August 2023)
35. ClinicalTrials.gov. Zemedy Application for Irritable Bowel Syndrome. https://classic.clinicaltrials.gov/ct2/show/study/NCT04723056?term=zemedy&draw=2&rank=1 (2022, accessed 20 August 2023)
36. Acceptability and Efficacy of Zemedy App Versus Education and Relaxation Training App for IBS. https://classic.clinicaltrials.gov/ct2/show/study/NCT04665271?term=zemedy&draw=2&rank=2 (2023, accessed 20 August 2023)
37. National Institute for Health and Care Excellence. Sleepio to treat insomnia and insomnia symptoms. https://www.nice.org.uk/guidance/mtg70/chapter/2-The-technology. (2022, accessed 20 February 2023).
38. Big Health. Digital therapeutic sleepio™ yields 28% lower healthcare costs. https://www.bighealth.com/news/health-economic-evaluation-of-sleepio/. (2020, accessed 20 February 2023).
39. Espie CA, Emsley R, Kyle SD, et al. Effect of digital cognitive behavioral therapy for insomnia on health, psychological well-being, and sleep-related quality of life: a randomized clinical trial. *JAMA Psychiatry* 2019; 76: 21–30.
40. ClinicalTrials.gov. Improving Sleep and Learning in Rehabilitation After Stroke, Part 2 (INSPIRES-2). https://classic.clinicaltrials.gov/ct2/show/NCT05511285?term=sleepio&spons=big+health&draw=2 (2022, accessed 20 February 2023).
41. Wamba F, Queiroz S and M M. Responsible artificial intelligence as a secret ingredient for digital health: bibliometric analysis, insights, and research directions. *Inf Syst Front* 2021; 25: 1–6.
42. Liu B and Sundar SS. Should machines express sympathy and empathy? Experiments with a health advice chatbot. *Cyberpsychol Behav Soc Netw* 2018; 21: 625–636.
43. Rajkomar A, Dean J and Kohane I. Machine learning in medicine. *N Engl J Med* 2019; 380: 1347–1358.
44. Norori N, Hu Q, Aellen FM, et al. Addressing bias in big data and AI for health care: a call for open science. *Patterns* 2021; 2: 100347.
45. Choi MJ, Kim H, Nah HW, et al. Digital therapeutics: emerging new therapy for neurologic deficits after stroke. *J Stroke* 2019; 21: 242.
46. Owens ME and Beidel DC. Can virtual reality effectively elicit distress associated with social anxiety disorder? *J Psychopathol Behav Assess* 2015; 37: 296–305.
47. Romero-Ayuso D, Toledano-González A, Rodríguez-Martínez MD, et al. Effectiveness of virtual reality-based interventions for children and adolescents with ADHD: a systematic review and meta-analysis. *Children* 2021; 8: 70.
48. Clus D, Larsen ME, Lemey C, et al. The use of virtual reality in patients with eating disorders: systematic review. *J Med Internet Res* 2018; 20: e157.
49. Ahmadpour N, Randall H, Choksi H, et al. Virtual reality interventions for acute and chronic pain management. *Int J Biochem Cell Biol* 2019; 114: 105568.
50. Gussoni G, Ravot E, Zecchina M, et al. Digital therapeutics in oncology: findings, barriers and prospects. A narrative review. *Ann Res Oncol* 2022; 2: 55–69.
51. Zeng Y, Zhang JE, Cheng AS, et al. Meta-analysis of the efficacy of virtual reality–based interventions in cancer-related symptom management. *Integr Cancer Ther* 2019: 18.
52. Freeman D, Reeve S, Robinson A, et al. Virtual reality in the assessment, understanding, and treatment of mental health disorders. *Psychol Med* 2017; 47: 2393–2400.
53. Xiao S, Angjeli E, Wu HC, et al. Randomized controlled trial of a dichoptic digital therapeutic for amblyopia. *Ophthalmology* 2022; 129: 77–85.
54. U.S. Food and Drug Administration. FDA authorizes marketing of virtual reality system for chronic pain reduction. https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-virtual-reality-system-chronic-pain-reduction. (2021, accessed 17 January 2023)
55. ClinicalTrials.gov. Luminopia one amblyopia vision improvement study. https://clinicaltrials.gov/ct2/show/NCT03608150 (2020, accessed 20 August 2023)
56. ClinicalTrials.gov. Luminopia One Pilot Study. https://classic.clinicaltrials.gov/ct2/show/NCT02782117. (2020, accessed 20 February 2023).
57. Garcia LM, Birckhead BJ, Krishnamurthy P, et al. An 8-week self-administered at-home behavioral skills-based virtual reality program for chronic low back pain: double-blind, randomized, placebo-controlled trial conducted during COVID-19. *J Med Internet Res* 2021; 23: e26292.
58. ClinicalTrials.gov. RelieVRx for Total Knee Arthroplasty (TKA) for the Reduction of Acute Postoperative Pain and Opioid Use. https://classic.clinicaltrials.gov/ct2/show/NCT04010266?term=RelieVRx&draw=2&rank=1. (2022, accessed 20 February 2023).

59. ClinicalTrials.gov. Virtual Reality for Chronic Pain and Opioid Use Disorder Pilot. https://classic.clinicaltrials.gov/ct2/show/NCT05546749?term=RelieVRx&draw=2&rank=2. (2023, accessed 20 February 2023).
60. Semerci R, Akgün Kostak M, Eren T, et al. Effects of virtual reality on pain during venous port access in pediatric oncology patients: a randomized controlled study. *J Pediatr Oncol Nurs*. 2021;38:142–151.
61. U.S. Food and Drug Administration. *Software as a medical device (SaMD)*. https://www.fda.gov/medical-devices/digital-health-center-excellence/software-medical-device-samd. (2018, accessed 15 January 2023)
62. Federal Institute for Drugs and Medical Devices. DiGA digital health applications. https://www.bfarm.de/EN/Medical-devices/Tasks/DiGA-and-DiPA/Digital-Health-Applications/_node.html (nd, accessed 24 December 2022)
63. Official Journal of the European Union. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and93/42/EEC. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=uriserv:OJ.L_.2017.117.01.0001.01.ENG. (2020, accessed 24 December 2022)
64. Gussoni G. Digital therapeutics: an opportunity for Italy, and beyond. *Tendenze Nuove* 2021; 4: 3–8.
65. Crisafulli S, Santoro E, Recchia G, et al. Digital therapeutics in perspective: from regulatory challenges to post-marketing surveillance. *Front in Drug Saf Regul* 2022; 2: 900946.
66. European Parliament. Single market for digital therapeutics. https://www.europarl.europa.eu/doceo/document/P-9-2022-003581_EN.html. (2022, accessed 15 January 2023).
67. EIT Health. The DiGAs framework– a model for europe? https://eithealth.eu/wp-content/uploads/2022/03/The-DiGAs-framework-a-model-for-Europe.pdf. (2021, accessed 24 December 2022).
68. Dahlhausen F, Zinner M, Bieske L, et al. There's an app for that, but nobody's using it: insights on improving patient access and adherence to digital therapeutics in Germany. *Digit Health* 2022: 8.
69. Richter JG, Chehab G, Stachwitz P, et al. One year of digital health applications (DiGA) in Germany–Rheumatologists' perspectives. *Front Med* 2022; 9: 1000668.
70. Wollsching-Strobel M, Butt U, Majorski DS, et al. Die digitalisierung der pneumologie und die rolle der fachgesellschaften [the digitalization of pneumology and the role of medical societies]. *Pneumologie* 2022; 76: 560–567.
71. Kadakia K, Patel B and Shah A. Advancing digital health: FDA innovation during COVID-19. *Npj Digit Med* 2020; 3: 161.
72. U.S. Food and Drug Administration. Premarket Notification 510(k). https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-notification-510k. (2022, accessed 10 September 2023).
73. U.S. Food and Drug Administration. Digital health center of excellence. https://www.fda.gov/medical-devices/digital-health-center-excellence. (2023, accessed 24 February 2023).
74. Ho A and Quick O. Leaving patients to their own devices? Smart technology, safety and therapeutic relationships. *BMC Med Ethics* 2018; 19: 1–6.
75. European Data Protection Supervisor. Digital therapeutics (DTx). European Data Protection Supervisor. https://edps.europa.eu/press-publications/publications/techsonar/digital-therapeutics-dtx_en. (nd, accessed 12 December 2022).
76. Refolo P, Sacchini D, Raimondi C, et al. Ethics of digital therapeutics (DTx). *Eur Rev Med Pharmacol Sci* 2022; 26: 6418–6423.
77. Kim S, Eom J and Shim J. A comparative study on intention to use digital therapeutics: mZ generation and baby Boomers' digital therapeutics use intention in Korea. *Int J Environ Res Public Health* 2022; 19: 9556.
78. Lutz J, Offidani E, Taraboanta L, et al. Appropriate controls for digital therapeutic clinical trials: a narrative review of control conditions in clinical trials of digital therapeutics (DTx) deploying psychosocial, cognitive, or behavioral content. *Front Digit Health* 2022; 4: 823977.
79. Tarricone R, Petracca F, Ciani O, et al. Distinguishing features in the assessment of mHealth apps. *Expert Rev Pharmacoecon Outcomes Res* 2021; 21: 521–526.
80. Kario K, Nomura A, Harada N, et al. Efficacy of a digital therapeutics system in the management of essential hypertension: the HERB-DH1 pivotal trial. *Eur Heart J* 2021; 42: 4111–4122.
81. Ravizza A, Ciani O, Ferrari A, et al. Clinical evaluation of digital therapeutics. *Tendenze* 2021: 72–104.
82. Babic B, Gerke S, Evgeniou T, et al. Algorithms on regulatory lockdown in medicine. *Science* 2019; 366: 1202–1204.
83. Meskó B and Topol EJ. The imperative for regulatory oversight of large language models (or generative AI) in healthcare. *NPJ Digit Med* 2023; 6: 120.
84. Saab K, Tu T, Weng WH, et al. Capabilities of gemini models in medicine. arXiv preprint arXiv:2404.18416. 2024.
85. Wachter RM and Brynjolfsson E. Will generative artificial intelligence deliver on its promise in health care? *Jama* 2024; 331: 65–69.
86. Yim D, Khuntia J, Parameswaran V, et al. Preliminary evidence of the use of generative AI in health care clinical services. Systematic narrative review. *JMIR Med Inform* 2024; 12: e52073.
87. Schaeffer D, Berens EM, Vogt D, et al. Health literacy in Germany: findings of a representative follow-up survey. *Deutsches Aerzteblatt Int* 2021; 118: 723.
88. De Santis KK, Jahnel T, Sina E, et al. Digitization and health in Germany: cross-sectional nationwide survey. *JMIR Public Health Surveill* 2021; 7: 11.