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Research article

A comprehensive survey of the clinical trial Landscape on digital therapeutics

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ABSTRACT

Background: Digital therapeutics (DTx) is an emerging and groundbreaking medical intervention that utilizes health software to treat or alleviate various diseases, disorders, conditions, or injuries. Although the potential of digital therapy is enormous, it is still in its nascent stage and faces multiple challenges and obstacles. The purpose of this study is to provide an overview of all DTx-related clinical trials in ClinicalTrials.gov and to promote the advancement of DTx.

Methods: Two reviewers and one expert evaluated data from all DTx clinical trials on ClinicalTrials.gov as of August 8, 2023. Trials utilizing digital therapeutics independently or in combination with traditional approaches were included. Incomplete trials and those lacking an evidence-based foundation were excluded. Basic information about product launches and primary outcome measures was extracted and analyzed.

Results: A total of 280 eligible trials were categorized into treating a disease (141, 50.4 %), managing a disease (120, 42.9 %), and improving a health function (19, 6.8 %). The focus was primarily on mental and behavioral disorders, neurological disorders, and endocrine, nutritional, and metabolic disorders. The number of trials has been increasing annually, yet trial design and conduct remain inconsistent. Randomized controlled trials (RCTs) accounted for 67.5 % of completed trials, and 36 trials (12.9 %) involved products already approved for marketing.

Conclusions: The growth in clinical studies on DTx underscores their potential in healthcare. However, challenges persist in standardization, regulation, and clinical efficacy. There is a need for a harmonized global classification of digital therapeutics and standardized clinical trial protocols to ensure efficacy and improve healthcare services.

1. Introduction

In recent years, the term Digital therapeutics (DTx) has become increasingly frequent in the medical field and has become an important development direction combining digital technology with medical technology [1–4]. For the origin of digital therapeutics, whether from a commercial or technical perspective, many organizations or media believe that it was in 2017,while in 2010, the US

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Food and Drug Administration (FDA) had approved the first prescription digital therapeutics product - BlueStar ® Diabetes management platform [5]. The name DTx officially appeared in 2012, and Click Therapeutics in the United States applied for the 'Digital Therapeutics' trademark to the United States Patent and Trademark Office [6]. Cameron Sepah et al. mentioned 'digital therapeutics' in a peer-reviewed publication in 2015, and defining it as 'improving the accessibility and effectiveness of healthcare through evidence-based behavioral therapy provided online' [7]. In 2017, the International Digital Therapeutics Alliance (DTA), was established and proposed the definition, industry standards, and regulatory guidelines of DTx, which were subsequently widely applied [8]. Since the concept of DTx was proposed by DTA in 2017, driven by the COVID-19 pandemic in 2020, it has emerged globally and entered commercial validation in 2021. However, based on the definition of DTA, for decision-makers and payers, It is still difficult to clearly distinguish digital therapeutics products from other digital health products (such as for clinical decision support, monitoring, diagnosis) and medical devices (such as Software as a Medical Device [SaMD] and Software in Medical Device [SiMD]). Therefore, in collaboration with the International Organization for Standardization (ISO), DTA first provided a consistent definition in industry and globally in June 2023 [9]: digital therapeutics is 'health software that treats or alleviates diseases, disorders, conditions, or injuries by generating and providing medical interventions that have a significant positive therapeutic impact on patient health'. And further defined the scope of use of digital therapeutics products: international jurisdictions can consider digital therapeutics products as medical devices; digital therapeutics products can be integrated with auxiliary components such as hardware platforms (mobile phones, tablets, computers, watches, headworn devices, etc.), input and output devices (wearable devices, sensors, etc.), drugs, and other supporting components to form a DTx system; digital therapeutics can be used as an independent therapy or combined with other traditional clinical interventions; digital therapeutics products include secondary and tertiary prevention content; From the perspective of the entire industry life-cycle, digital therapeutics is still in its early stages of development globally.

With the rapid development of DTx products and significant market prospects, there are many unknown factors and challenges in concept recognition, technical regulation, clinical application, commercial implementation, and other aspects in the future. Clinical trials provide a reliable scientific evaluation framework for new medical interventions or products. This study summarizes all clinical trials related to DTx in ClinicalTrials.gov, with the aim of promoting the further development of DTx.

2. Methods

2.1. Search strategy and selection criteria

We conducted a comprehensive search for information on all clinical trials registered on the ClinicalTrials.gov website by August 8, 2023. Although the formal definition of digital therapeutics emerged in 2017, we aimed to systematically evaluate trials that involved digital software interventions and were supported by evidence-based medical reasoning. To achieve this, we broadened the eligibility criteria to include trials utilizing the following terms: (1) Intervention/Treatment: "digital therapeutics" (1329) OR "digital intervention" (1712) OR "digital medicine" (549) OR "DTx" (25); (2) Other terms: "digital therapeutics" (6952) OR "DTx" (44). The goal of these search strategies was to identify all clinical trials aligning with the characteristics of digital therapeutics.

We included trials that were: (i) completed trials, including independent trials that tested the same digital therapeutics product using different methods; (ii) trials in which the healthcare intervention was delivered through software; (iii) trials in which the intervention was delivered by software through a technology platform, medical device, or medication; and (iv) trials in which the intervention was used for the treatment, management, or prevention of a disease or condition.

We excluded trials that were (i) duplicates found through both search strategies; (ii) incomplete trials (e.g., active not recruiting, available, enrolling by invitation, no longer available, not yet recruiting, recruiting, suspended, terminated, unknown, withdrawn); (iii) trials that did not use the software as an intervention; and (iv) trials that were conducted only by clinicians and provided only notification, monitoring or diagnostic information.

The 280 eligible trials included in our analysis are detailed in Supplementary Table S1.

2.2. Data screening

We downloaded the obtained studies in comma-separated value files and converted them into Excel workbooks. Initially, one evaluator (YH) screened for trials with software interventions that fell under the "digital health" category, based on the Title and Intervention. Subsequently, two assessors (ZXK and ZXY) independently screened trials that more closely aligned with the definition of digital therapeutics, focusing on the Title and Brief Summary. Any discrepancies were resolved through discussion, with a third assessor (YH) involved when necessary. This preliminary assessment accounted for approximately 17.7 % of the included digital health studies.

2.3. Data extraction and analysis

One evaluator (YH) utilized agreed-upon data points to extract the following information for all clinical trials related to digital therapeutics: NCT Number, Conditions, Interventions, Primary Outcome Measures, Secondary Outcome Measures, Other Outcome Measures, Sponsor, Collaborators, Enrollment, Funder Type, Study Type, Study Design, Start Date, Completion Date, and Locations. Furthermore, we extracted the trial's title and abstract and synthesized the aforementioned information to document the key functions of the digital therapeutics that the trial focused on, including disease treatment, disease management, and improvement of specific health functions. For each trial's set of registration conditions, we collected the year the trial was initiated, the duration in study days,

and the corresponding country. Additionally, we recorded the primary diseases and symptoms mentioned in the trial's Conditions and cross-referenced them with the International Classification of Diseases, 10th Revision (ICD-10) to determine the appropriate ICD-10 chapter code for each ailment. This cross-referencing process was manually conducted by an evaluator (ZXK), taking into account the name of the original Conditions, their specifications, and their position within the hierarchy. Any unmatched codes were identified by another assessor (YH) who actively participated in the ensuing discussions. An evaluator (ZXY) extracted and confirmed the product name and listing information for the clinical trial through the DTA listed product website, as well as the product registration and approval information provided by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) websites. Internet searches were also conducted to gather additional information.

The primary endpoint outcomes of DTx typically fall into one of eight different categories: (1) Biological & Pharmacological: this category centers on evaluating the effects of digital therapeutics on biological and pharmacological indicators, including physiological parameters, biochemical indicators, and pharmacokinetic parameters. (2) Patient Compliance & Adherence: this category assesses the extent to which patients adhere to and comply with the prescribed use of digital therapeutics, ensuring adherence to the intended treatment plan. (3) Patient-reported Outcomes: the effectiveness of digital therapeutics is evaluated through subjective patient reports, encompassing feedback on treatment satisfaction, pain assessment, and similar subjective assessments. (4) Primary Efficacy Improvements: this category focuses on the degree to which digital therapeutics enhance the primary symptoms or clinical indicators of

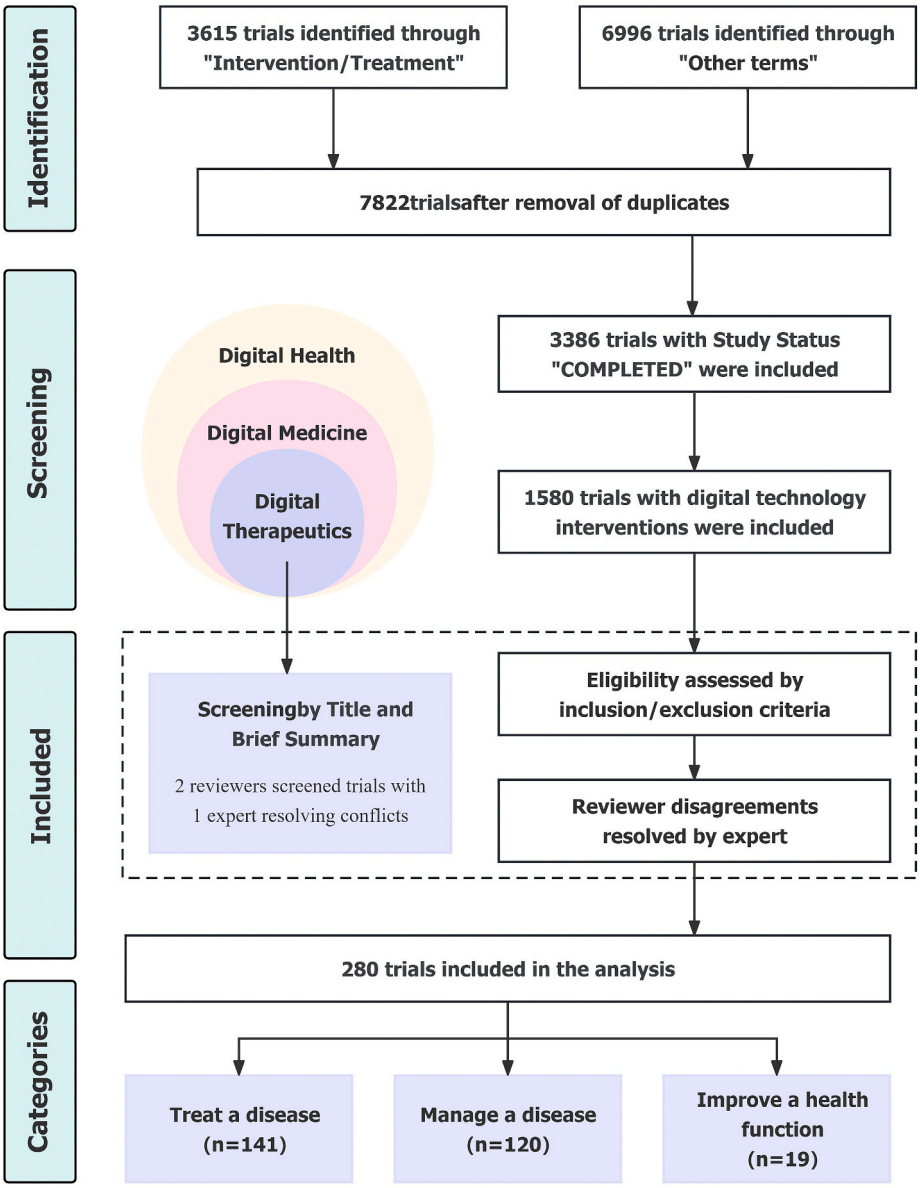

Fig. 1. Flow Diagram of Selection of ClinicalTrials.gov Records. *Note.* The search for records was conducted on August 8, 2023.

the disease. (5) Quality of Life: this category aims to gauge the impact of digital therapeutics on patients' daily quality of life and mental health. (6) Safety: this category concentrates on assessing the safety of digital therapeutics for patients, encompassing the impact of adverse events and side effects. (7) System Usability: this category evaluates the ease of use and user experience of digital therapeutics devices or systems, ensuring their effectiveness and convenience in clinical practice. (8) Technical Performance: this category focuses on the performance of the digital therapeutics device or technology, including assessments of accuracy, stability, and sensitivity. These eight outcomes can be extracted and grouped into three broad categories of clinical outcome-related, patient-reported-related, and technology-related outcomes.

3. Results

Based on the above search strategy, we screened the included 7822 eligible trials according to predefined criteria. Initially, we excluded trials with statuses such as "active not recruiting" (429), "available" (2), "enrolling by invitation" (119), "no longer available" (1), "not yet recruiting" (675), "recruiting" (1889), "suspended" (26), "terminated" (316), "unknown" (813), "withdrawn" (162), and "others" (4) in order to retain only completed trials, resulting in the exclusion of 3386 trials. We further excluded trials that did not involve digital therapeutics interventions, leading to a total of 1806 trials being excluded. After excluding trials that were not part of digital health based on their titles, we were left with 757 trials. Finally, through screening the brief summary, we retained 280 trials (Fig. 1).

4. Developments in clinical trial research for DTx

In general, the development of digital therapeutics can be conceptually divided into three distinct phases based on the analysis presented in Fig. 2: the "embryonic stage," the "exploration stage," and the "rapid development stage."

The first phase, known as the "embryonic stage" (2002–2016), represents the early conceptual stage of digital therapeutics. During this phase, people had not yet realized the potential of digital therapeutics, but research and development efforts had already begun. The embryonic period started around 2002 and continued until 2017 when the concept of digital therapeutics became more formalized. The second phase, called the "exploration stage" (2017–2020), marks the formal introduction and growing attention towards digital therapeutics. During this phase, the application fields of digital therapeutics expanded beyond specific medical domains and began to include various areas such as mental health and chronic diseases. This period witnessed a gradual increase in the adoption and recognition of digital therapeutics. The third phase, known as the "rapid development stage" (2020-present), was primarily driven by the impact of the COVID-19 pandemic, which accelerated the advancement of digital therapeutics. As a result of the limitations imposed by the pandemic, online consultations and remote diagnosis and treatment gained widespread acceptance, making digital therapeutics a popular choice. Additionally, during this phase, the technology supporting digital therapeutics, including augmented reality and virtual reality, underwent significant updates and improvements. The rapid development period began around 2020 and continues to the present day.

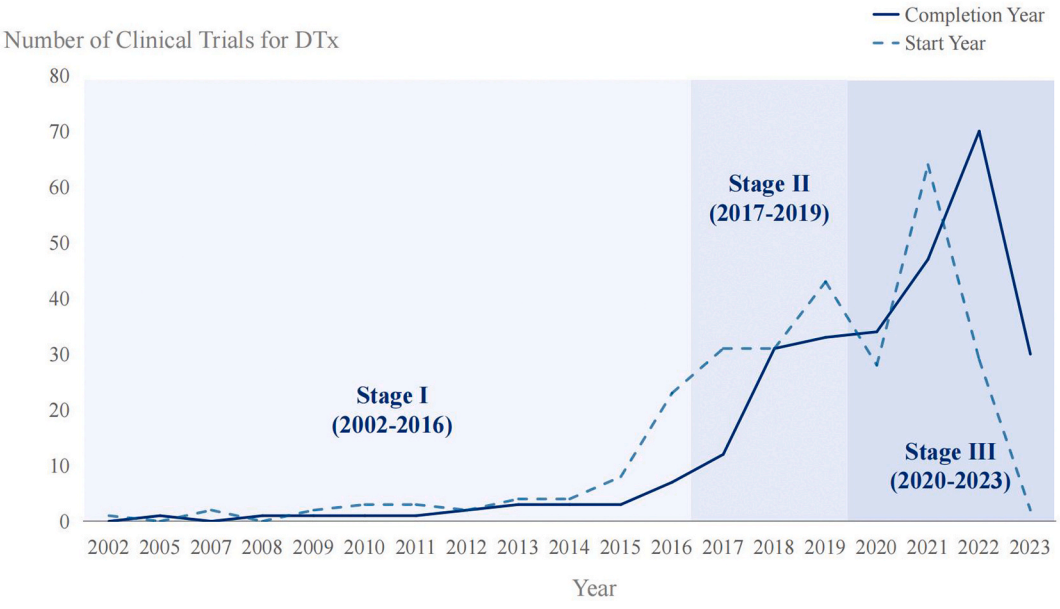

Fig. 2. Line graph of enrollment versus completed clinical trials of digital therapeutics per year. *Note.* The solid lines indicate the completion year of the trials, while the dashed lines represent the start year of the trials.

4.1. Global DTx clinical trial development

The registered and completed digital therapeutics trials primarily focus on Mental and Behavioral Disorders, Diseases of the Nervous System, and Endocrine, Nutritional, and Metabolic Diseases, which collectively account for 59.3 % of the total trials conducted. Within the Mental and Behavioral Disorders category, clinical trials mainly target depression, anxiety disorders, schizophrenia, bipolar disorder, sleep disorders, and more. These trials involve techniques such as visual stimulation, eye movement, and fine vision to aid in treatment. In the Diseases of the Nervous System category, clinical trials mainly address conditions like stroke, brain injury, and brain damage. Specifically, the trials in this category primarily aim to assist patients with mild cognitive dysfunction resulting from stroke, cerebral function injury, Parkinson's disease, and other related conditions by providing cognitive rehabilitation training. The Endocrine, Nutritional, and Metabolic Diseases category primarily focuses on chronic diseases such as diabetes mellitus, hypertension, and obesity. The digital therapeutics trials in this category offer functions for physiological indicators collection, monitoring, warning, as well as calculation and management. Additionally, doctors can remotely monitor patients' indicators, enabling them to understand the patient's condition and make timely adjustments to the treatment plan(Supplementary Fig. S1).

Fig. 3 and Supplementary Table S2 depicts the geographic distribution of trials of digital therapeutics, highlighting notable regional variations. Trials of relevance were more frequently conducted in North America (145) and Europe (92), with fewer taking place in Asia (39). The highest number of trials was carried out in the United States, accounting for 136 cases, which is nearly half (48.6 %) of all trials. This was followed by the United Kingdom (5.7 %), Spain (4.6 %), Turkey (4.3 %), France (3.9 %), Korea (3.6 %), Canada (3.2 %), Sweden (3.2 %), and China (2.9 %). Additionally, the median time from start to finish of trials was 327.5 (IQR, 176.5–562.75) days (Supplementary Fig. S2). For trials targeting digital therapeutics (Supplementary Fig. S3), the median number of patients enrolled in each trial was 68 (IQR, 33.75–147.25).

4.2. Current status and characteristics of DTx clinical trial designs Worldwide

The rapid development of digital therapeutics has been accompanied by an imbalance and inadequacy in the design and conduct of their trials (Table 1, Fig. 4). According to the DTA2021 classification criteria, digital therapeutics can be classified as treating a disease (141, 50.4 %), managing a disease (120, 42.9 %), and improving a health function (19, 6.8 %). The majority of trials were INTERVENTIONAL (264, 94.3 %) and RANDOMIZED (189, 67.5 %). Among the Intervention Models, PARALLEL (179, 63.9 %) accounted for the highest percentage, followed by SINGLE GROUP (64, 22.9 %). Notably, 76.4 % (n = 214) of these trials were initiated by academic institutions/universities (hospitals), 19.6 % (n = 55) were initiated by industry sponsors, and 3.9 % (n = 11) were initiated by the government/FED.

4.3. Marketed DTx product Features

Among the digital therapeutics clinical trials retrieved from ClinicalTrials.gov, 36 (12.9 %) trials involved products that have already been approved for marketing and still address prevention, treatment, and rehabilitation aspects (Table 1, Supplementary Table S3). DTx stands out from ordinary health management services due to its adherence to medical guidelines and clinical validation as a unique developmental advantage. However, blinding and randomization of DTx are usually more challenging compared to

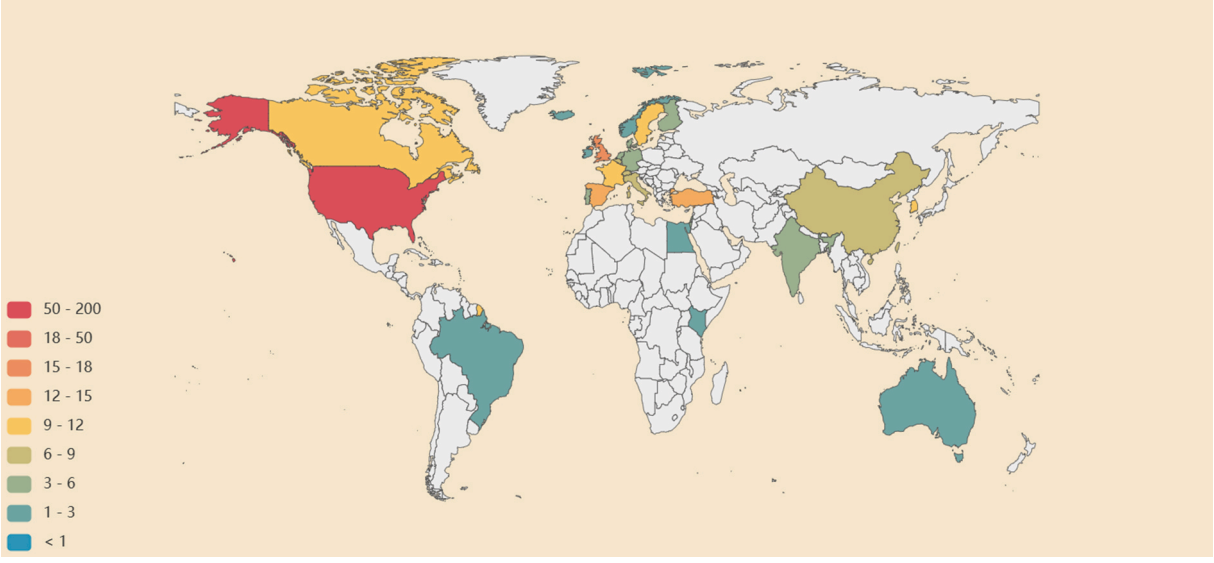

Fig. 3. World map of the number of digital therapeutics trials conducted.

Table 1
Comparison of design characteristics of Launched and Unlaunched DTx trials registered on ClinicalTrials.gov.

	Overall	Launched DTx[a]	Unlaunched DTx
	(N = 280)	(N = 36)	(N = 244)
DTx Type			
Improve a health function	19 (6.8 %)	4 (11.1 %)	15 (6.1 %)
Manage a disease	120 (42.9 %)	20 (55.6 %)	100 (41.0 %)
Treat a disease	141 (50.4 %)	12 (33.3 %)	129 (52.9 %)
Study Type			
INTERVENTIONAL	264 (94.3 %)	35 (97.2 %)	229 (93.9 %)
OBSERVATIONAL	16 (5.7 %)	1 (2.8 %)	15 (6.1 %)
Start Phases			
2002–2016	52 (18.6 %)	4 (11.1 %)	48 (19.7 %)
2017–2019	105 (37.5 %)	14 (38.9 %)	91 (37.3 %)
2020–2023	123 (43.9 %)	18 (50.0 %)	105 (43.0 %)
Region			
North America	145 (51.8 %)	18 (50.0 %)	127 (52.0 %)
Europe	92 (32.9 %)	15 (41.7 %)	77 (31.6 %)
Asia and others[b]	43 (15.4 %)	3 (8.3 %)	40 (16.4 %)
Funder Type			
Academic institutions & universities (hospitals)	214 (76.4 %)	21 (58.3 %)	193 (79.1 %)
Government & FED	11 (3.9 %)	0 (0 %)	11 (4.5 %)
Industry	55 (19.6 %)	15 (41.7 %)	40 (16.4 %)
Category			
Diseases of the circulatory system	13 (4.6 %)	3 (8.3 %)	10 (4.1 %)
Diseases of the musculoskeletal system and connective tissue	17 (6.1 %)	1 (2.8 %)	16 (6.6 %)
Diseases of the nervous system	45 (16.1 %)	4 (11.1 %)	41 (16.8 %)
Diseases of the respiratory system	11 (3.9 %)	3 (8.3 %)	8 (3.3 %)
Endocrine, nutritional and metabolic diseases	30 (10.7 %)	4 (11.1 %)	26 (10.7 %)
Factors influencing health status and contact with health services	14 (5.0 %)	0 (0 %)	14 (5.7 %)
Mental and behavioral disorders	91 (32.5 %)	8 (22.2 %)	83 (34.0 %)
Neoplasms	15 (5.4 %)	4 (11.1 %)	11 (4.5 %)
Others[c]	44 (15.7 %)	9 (25.0 %)	35 (14.3 %)
Enrollment			
<50	103 (36.8 %)	14 (38.9 %)	89 (36.5 %)
50-100	79 (28.2 %)	9 (25.0 %)	70 (28.7 %)
101-150	29 (10.4 %)	4 (11.1 %)	25 (10.2 %)
>150	69 (24.6 %)	9 (25.0 %)	60 (24.6 %)
Allocation			
NON_RANDOMIZED	91 (32.5 %)	18 (50.0 %)	73 (29.9 %)
RANDOMIZED	189 (67.5 %)	18 (50.0 %)	171 (70.1 %)
Intervention Model			
OBSERVATIONAL and OTHERS	37 (13.2 %)	3 (8.3 %)	34 (13.9 %)
PARALLEL	179 (63.9 %)	20 (55.6 %)	159 (65.2 %)
SINGLE_GROUP	64 (22.9 %)	13 (36.1 %)	51 (20.9 %)
Endpoint [d]			
Clinical efficacy-related	81 (28.9 %)	10 (27.8 %)	71 (29.1 %)
Patient-related outcomes	182 (65.0 %)	19 (52.8 %)	163 (66.8 %)
Technical-related	17 (6.1 %)	7 (19.4 %)	10 (4.1 %)
Mask			
DOUBLE, TRIPLE,QUADRUPLE	46 (16.4 %)	3 (8.3 %)	43 (17.6 %)
NONE	166 (59.3 %)	27 (75.0 %)	139 (57.0 %)
SINGLE	68 (24.3 %)	6 (16.7 %)	62 (25.4 %)

Note.

[a] "Launched DTx" refers to digital therapeutics products that have been identified as commercially available and are currently on the market. "Unlaunched DTx" includes products that, as of our search, have not been found to be publicly available for purchase or use.

[b] The "others" in Region include Africa(2), Oceania(1) and South America(1).

[c] The "others" in Category include Diseases of the genitourinary system, Diseases of the digestive system, Diseases related to 2019 Diseases of the genitourinary system, Diseases of the digestive system, Diseases related to 2019 novel coronavirus (COVID-19), External causes of morbidity and mortality, Injury, poisoning and certain other consequences of external causes, Diseases of the blood and blood-forming organs Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, Diseases of the eye and adnexa, Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere abnormal clinical and laboratory findings, not elsewhere classified, Certain conditions originating in the perinatal period, Human Certain conditions originating in the perinatal period, Human immunodeficiency virus disease, Pregnancy, childbirth and the puerperium.

[d] Clinical efficacy-related includes Biological&Pharmacological, Primary Efficacy Improvements, Patient compliance/adherence and Safety. Patient reported-related include Patient-reported outcomes and Quality of life. Technical-related includes System Usability and Technical Performance.

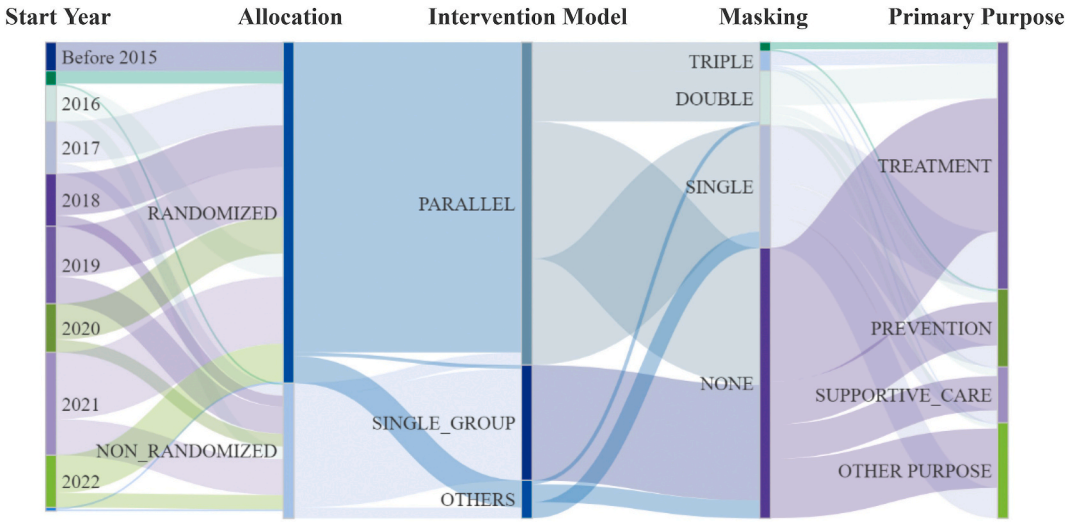

Fig. 4. Sankey diagram for clinical trial studies of digital therapeutics. Note. This Sankey diagram is utilized to analyze the trends in the "Start Year," "Allocation," "Intervention Model," "Masking," and "Primary Purpose" of DTx clinical trials. As of August 8, 2023, a total of 280 clinical trials related to digital therapeutics were identified on ClinicalTrials.gov using relevant keywords. These clinical trials comprise primarily of "INTERVENTIONAL" studies and "RANDOMIZED" trials. The "Intervention Models" are categorized as follows: "PARALLEL", "SINGLE GROUP", and "OTHERS". The "Masking" types include "TRIPLE," "DOUBLE," "SINGLE," and "NONE." The "Primary Purpose" encompasses "PREVENTION," "TREATMENT," "SUPPORTIVE CARE," and "OTHER PURPOSE."

traditional RCTs. Out of the approved DTx products included in this study, 50 % were clinically evaluated through RCTs, while the other half used existing or retrospective real-world data for clinical evaluation. Due to the current immaturity of the DTx industry, there is no standardized system for clinical design, and the therapeutic area and clinical focus vary from product to product. Currently marketed products are gradually paying more attention to system performance indicators such as System Usability and Technical Performance, while less attention is given to patient-reported outcomes and safety (Supplementary Fig. S4). Industry-driven DTx products (41.7 %) enjoy the advantage of being first-to-market.

5. Discussion

Although the number of clinically registered trials for digital therapeutics has been steadily increasing since the formal introduction of the concept of "digital therapeutics" in 2017, the impact of the COVID-19 outbreak has further accelerated this trend. It is noteworthy that the digital therapeutics registered in clinical trials align closely with the predominant scope of application for approved products currently on the market. The focus remains largely centered on the psychiatric field and chronic disease management [10,11]. Furthermore, a significant proportion of clinical trials are characterized by small sample sizes. DTx, as a novel medical device, has made strides in application, but confronts numerous challenges, including the definition of comprehensive species classification, clinical trial design, and marketing regulations [12,13].

DTx must adhere to an evidence-based approach, requiring appropriate medical evidence based on the level of risk involved. Therefore, designing clinical trials is crucial to obtain a high level of evidence for DTx. Randomized Controlled Trials (RCTs) are considered to provide the highest level of evidence among various levels [14]. Thus, designing RCTs is vital in evaluating the effectiveness and safety of DTx. While DTx and other digital health products are accessible as mobile apps, DTx specifically targets certain medical conditions [15,16]. When designing an RCT for DTx, it is important to define the trial's objectives, expected effects, and select an appropriate control group, such as conventional treatment, placebo, or other established effective treatments. The trial should follow strict randomization principles to ensure even distribution of participants across groups. It is also necessary to determine outcome indicators, duration and observation periods, as well as data collection and analysis methods. However, due to the nature of DTx products, RCTs may not be applicable in all cases and may encounter ethical or implementation constraints. In this study, only 67.5 % (189) of the clinical trials adopted RCTs. Therefore, when designing clinical trials for DTx, other trial designs need to be comprehensively considered and flexibly selected on a case-by-case basis [17,18].

However, there are currently no unified guidelines for clinical trials of digital therapeutics products. Although the Digital Therapeutics Alliance (DTA) will soon launch an accreditation program for digital therapeutics products through DirectTrust, utilizing existing standards for device privacy, security, and interoperability to establish criteria for evaluating the efficacy of digital therapeutics [19]. These guidelines only provide general recommendations on trial design, data collection, and analysis. Due to the diversity and complexity of DTx products, they need to be flexibly adapted and applied on a case-by-case basis. To address this, academia and regulatory bodies need to collaborate to develop harmonized and standardized trial methodologies applicable to digital therapeutics. These guidelines or norms should include the following aspects: (1) Standards for clinical trial design: Clear design principles and

methods for clinical trials of digital therapeutics should be established. This includes determining the sample size, selecting the control group, using randomization methods, implementing blinding techniques, and considering other key elements. (2) Criteria for trial implementation: The process and methods for conducting clinical trials of digital therapeutics should be specified. This involves outlining the specific operations for each stage, such as subject recruitment, screening procedures, drug administration protocols, and follow-up requirements. (3) Standards for data analysis and result reporting: Standardized data analysis methods for digital therapeutics clinical trials should be defined. This includes specific requirements for data processing, statistical analysis, and result reporting. By formulating these guidelines or norms, the consistency and standardization of digital therapeutics clinical trials can be ensured, leading to improved efficiency and success rates in digital therapeutics research and development. Additionally, these guidelines will assist regulators in effectively supervising and evaluating digital therapeutics, safeguarding the safety and rights of patients.

After completing the clinical trial of DTx, several internal and external challenges still need to be addressed to drive the commercialization of digital therapeutics products [20]. Digital therapeutics aim to transform and innovate traditional healthcare services through digital technology, providing more accurate, convenient, and personalized healthcare services. Clinical trials play a crucial role in the research, development, and commercialization process of digital therapeutics products by assessing their safety, efficacy, and feasibility, thus providing a scientific basis for product launch. It has been observed that most marketed DTx products are led by companies or enterprises. This can be attributed to the significant investments and resources required for the R&D and commercialization of digital therapeutics, which companies or enterprises often possess due to their stronger financial strength and marketing capabilities. Furthermore, DTx clinical trials impose higher requirements on digital technology. The use of Extended Reality (XR) and Human-computer Interaction Techniques (HCI) is gradually emerging in clinical trials. XR digital therapeutics primarily focus on providing patients with seamless transitions between virtual and real worlds, enabling "immersion" for assessment and treatment. Their applications include mental disorder treatment, disease rehabilitation, pain relief, visual impairment, and more [21–25]. HCI digital therapeutics integrate, analyze, retrieve, and consolidate healthcare data, offering effective decision support to patients and healthcare professionals by implementing evidence-based reasoning through electronic health record systems, decision-support systems, and outcome-feedback systems [26]. These two functions can also be combined to create richer interactive experiences, resulting in various DTx systems such as apps, wearables, AR/VR, and video games [27,28]. However, the application of these technologies is still in its early stages of development. Some clinical trials have low technical barriers and are limited to digitally-driven products. For instance, some trials solely rely on simple games or animations for mental illness treatment and generate assessment reports through fixed question-and-answer logics, indicating insufficient technical advancement of the products. It is crucial to foster interdisciplinary collaboration among medical experts, technicians, and marketers to drive the development and commercialization of digital therapeutics products [29].

LIMITATION.

Our study had several limitations that should be acknowledged. Firstly, our reliance solely on information provided by registrants on ClinicalTrials.gov may have resulted in the omission of study records where comprehensive details of the study design were not explicitly reported or kept up-to-date. This could have introduced potential bias or overlooked relevant information. Secondly, our focus was primarily on clinically registered trials, and we did not specifically analyze real-world studies of digital therapeutics as a separate category. In addition, when distinguishing between marketed and unlisted DTx products, it is possible that some of the products are still in the approval cycle due to the lack of information on the process and timing of approvals. As a result, we may have missed out on examining a subset of unregistered and pending marketing applications for digital therapeutics that could have provided valuable insights.

6. Conclusions

Digital Therapeutics, as a groundbreaking approach in healthcare, presents novel prospects for clinical research in disease prevention, diagnosis, treatment, and management. Anchored in evidence-based medicine, DTx holds the potential to significantly enhance the effectiveness of digital therapeutics in clinical settings and propel the advancement of high-quality healthcare service systems. However, current research has revealed notable inadequacies. There exists a lack of comprehensive, detailed, and unified classification of digital therapeutics on a global scale, with ambiguous definitions of DTx, alongside the absence of corresponding clinical trial specifications and standards for diverse technological modalities. Moreover, there is a need for further exploration of the methodologies and quality of related research designs. Looking ahead, it is imperative to elevate the technical proficiency of products, establish a robust public technical testing platform for digital therapeutics, reinforce regulatory oversight, standardize trials, ensure clinical efficacy, and bolster data security measures. These initiatives will wield considerable influence over decision-making in DTx clinical practice and elevate the quality of healthcare services by advancing evidence-based approaches.

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Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

CRediT authorship contribution statement

Han Yao: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Zirui Liao:** Conceptualization, Writing – original draft, Writing – review & editing. **Xinyi Zhang:** Data curation, Investigation. **Xiaoke Zhang:** Data curation, Investigation. **Mengyu Li:** Data curation, Investigation. **Lili You:** Conceptualization, Project administration, Supervision, Writing – review & editing. **Yuanli Liu:** Funding acquisition, Methodology, Supervision, Validation.

Declaration of competing interest

The authors declare no competing interests.

Appendix A. Supplementary data

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