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Mao, X.Y.; Zeng, D.; Wang, X.C.; Pearce, D.A.; Baynam, G.; Chavannes, N.H.; ... ; Wong, T.Y.

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Digital health technology use in clinical trials of rare diseases: a systematic review

Xiangyun Mao[1,2,23], Dian Zeng[3,23], Xiaocong Wang[3], David A. Pearce[4,5], Gareth Baynam[6,7,8,9], Niels H. Chavannes[10], Wendy K. Chung[11], Honghan Wu[12,13], Yih-Chung Tham[14,15,16,17], Shuyang Zhang[18,19] ✉, Guanqiao Li[1,2] ✉ & Tien Yin Wong[20,21,22] ✉

Abstract

Background Rare disease clinical trials face unique challenges, resulting in low enrollment and limited retention. Digital health technologies (DHTs), when applied through a patient-centric lens, offer promising solutions to these challenges by enhancing data collection efficiency, improving patient engagement, and supporting long-term health care.

Methods This study investigates DHT application in clinical studies across the ten most-studied rare diseases and was registered with PROSPERO (registration number: CRD420251088025). Up to June 26 2024, a total of 262 studies were identified through ClinicalTrials.gov, the International Clinical Trials Registry Platform, Cochrane Central Register of Controlled Trials, PubMed, and Web of Science. DHT applications were classified into patient recruitment, digital treatment, data monitoring and collection, outcome assessment, remote follow-up, and long-term care management based on scenarios and functionalities.

Results Among all DHT applications, data monitoring and collection was the most prevalent (31.3%), serving primarily to enable continuous tracking of physiological parameters relevant to specific rare disease conditions. Digital treatment is featured in 57 studies (21.8%), most commonly as digital physiotherapy. A notable increase in DHT adoption is observed from 2017–2020 to 2021–2024 across nearly all ten diseases. Between 2021 and 2024, cystic fibrosis shows the highest proportion of DHT-enabled trials relative to all studies conducted for that disease (29.7%).

Conclusions Our findings reveal a growing trend toward digital integration in rare disease trials to support decentralized, scalable, and patient-centered research models. We propose a "4A" conceptual framework—Accessibility, Agility, Awareness, and Adaptability to accelerate therapeutic development and expand access to care for these underserved rare disease populations.

Plain language summary

Hundreds of millions of people around the world live with rare diseases, but most of these conditions still don't have effective treatments. Clinical trials are vital for new therapies, but rare disease trials are especially challenging due to small, dispersed patient populations and difficulties with long-term participation. This study looked at how digital health tools—like wearable devices, mobile apps, and healthcare platforms—are being used to improve rare disease clinical trials. We analysed 262 trials across ten rare diseases and found that digital health technologies were increasingly used for remote monitoring, digital treatment, and long-term care. By making it easier for patients to participate in trials—no matter where they live—digital technologies can help speed up the development of much-needed treatments and help make research more inclusive and equitable by reaching patients who would otherwise be left out.

Rare diseases are a set of diseases characterized by extremely low prevalence, often involving genetic anomalies or unique pathophysiological mechanisms. Despite the rarity of each individual condition, rare diseases collectively affect over 400 million people worldwide[1]—approximately eight times the global number of cancer patients[2]. Recent estimates suggest there are more than 10,000 different types of rare diseases[1]; however, fewer than 5% of these conditions have approved treatments[3], underscoring a substantial yet frequently overlooked global health challenge.

Clinical trials are a critical step in the development of new treatments, serving to assess their efficacy and safety before receiving market approvals, yet they also represent the most resource-intensive and operationally complex stage[4]. In the context of rare diseases, the distinct characteristics of patient population introduce additional hurdles compared to trials for more common diseases (Table 1). Factors such as heterogeneous clinical manifestations, geographic dispersion, limited patient numbers and high disability rates exacerbate these challenges. In particular, clinical heterogeneity complicates the development of robust clinical endpoints, as small and

A full list of affiliations appears at the end of the paper. ✉e-mail: shuyangzhang103@nrdrs.org; guanqiaoli@tsinghua.edu.cn; ophwty@nus.edu.sg

Table 1 | Challenges in conducting clinical studies for rare diseases compared to common diseases

Stage in clinical trial	Common diseases	Rare diseases
Patient recruitment	Recruitment is typically more feasible due to larger, more accessible patient populations, allowing standard outreach methods to be effective.	Due to small, heterogeneous, and geographically dispersed patient populations, recruitment usually requires specialized referral networks and patient registry platforms.
Treatment	Treatments often aim for disease modification or cure, with clinical outcomes focusing on metrics such as survival or disease progression.	Most rare diseases lack effective treatments. Investigational therapies are commonly aimed at symptom relief.
Follow-up/ Retention	Participants are usually located in accessible, concentrated areas, making follow-up logistically manageable.	Participants are often dispersed across remote or underserved regions, making follow-up challenging due to logistical, transportation and accessibility barriers.
Data monitoring	Less frequent and more standardized monitoring is often sufficient due to predictable disease progression patterns and well-established clinical biomarkers.	More intensive and customized monitoring is often required due to clinical heterogeneity, and the absence of validated clinical indicators.
Clinical outcomes	Outcomes are typically easier to measure and interpret due to the widespread use of validated endpoints and standardized analysis methods.	Outcome assessment is often exploratory, challenged by small sample sizes, clinical variability, and limited understanding of disease mechanisms.
Long-term healthcare	Long-term care is relatively standardized, based on established protocols and predictable nature of diseases.	Long-term care is highly individualized, requiring dynamic care plans and continuous coordination to manage acute and fluctuating needs.

fragmented patient populations often lack sufficient data to establish reliable outcome measures. Furthermore, limited diagnostic capabilities, difficulty in identifying eligible patients, and variability in disease progression collectively contribute to low enrollment rates, prolonged study timelines, and compromised data integrity in rare disease trials, ultimately resulting in higher failure rates compared to non-rare disease trials[5,6]. These challenges continue to impede progress in delivering effective treatments to patients with rare diseases.

Amid rapid technological innovation, digital health technologies (DHTs) have garnered significant attention for their potential to transform clinical research by enhancing patient engagement, improving trial efficiency, and enabling personalized healthcare[7,8]. A core rationale for integrating DHTs lies in their capacity to enable patient-centric model of care[9], which prioritize accessibility, convenience, and individualized support[10]. Encompassing a wide range of tools, including artificial intelligence (AI), the Internet of Things, specialized healthcare software, sensors, and wearable devices[11], DHTs enable decentralized approaches to enhance patient participation and streamline trial operations[12]. In the rare disease context, these tools can help reach geographically dispersed patients while streamlining trial execution, thereby making rare disease trials more feasible and inclusive[13].

Despite these promising advancements, a systematic evaluation of how DHTs are integrated into rare disease trials remain lacking. To address this evidence gap, this study investigates the use of DHTs in rare disease clinical studies targeting the ten rare diseases with the highest levels of R&D activity. It characterizes these trials and analyzes the application of DHTs across multiple stages of study process, highlighting their functional roles, technological diversity, and opportunities for future improvements. The findings aim to provide actionable insights for policymakers, clinicians, researchers and patients to advance DHT-driven, patient-centric approaches, ultimately improving patient outcomes and addressing the unmet medical needs of rare disease populations worldwide, ensuring they have equitable access to innovative treatments and improved healthcare. Our analysis shows that data monitoring and collection is the most common use of DHT in rare disease trials, followed by digital treatment, primarily digital physiotherapy. We observe a notable increase in DHT adoption from 2017 to 2024 across nearly all disease areas, with cystic fibrosis showing the highest proportion of DHT-enabled trials. These findings highlight a growing shift toward decentralized and patient-centered trial models. We summarize this shift within a "4A" framework—Accessibility, Agility, Awareness, and Adaptability—designed to expand access to care for underserved rare disease populations.

Methods

Search strategy and selection criteria

The systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420251088025. Clinical trials utilizing DHTs in rare diseases were identified through searches on ClinicalTrials.gov, the International Clinical Trials Registry Platform (ICTRP), Cochrane Central Register of Controlled Trials, PubMed and Web of Science, with records collected up to June 26, 2024. Given the broad scope and varying definitions of rare diseases worldwide, our analysis focused on the top ten rare diseases with the highest levels of research and development (R&D) activity[14]. These included amyotrophic lateral sclerosis (ALS), pulmonary fibrosis (PF), acute respiratory distress syndrome (ARDS), Duchenne muscular dystrophy (DMD), cystic fibrosis (CF), Huntington's disease (HD), pulmonary hypertension (PH), cytokine release syndrome (CRS), frontotemporal dementia (FTD), and graft-versus-host disease (GVHD)., All selected diseases were confirmed to be classified as rare diseases by Orphanet (https://www.orpha.net/), a widely used global database for rare diseases. These ten diseases accounted for over 50% of recent R&D activity in the rare disease field[14]. This ensures that our selection, while limited in scope, captures key patterns in current rare disease trials.

To ensure comprehensive identification of DHT-enabled studies, we employed a set of 53 search terms related to DHTs, such as "digital health", "telemedicine", "artificial intelligence", "smartphone", "mobile device", and "wearable devices" (see Supplementary Table 1). Searches were limited to abstracts, titles, and summaries, and restricted to interventional studies. Non-interventional designs, including observational studies, patient registries, and expanded access reports, were excluded. No restrictions were applied regarding comparison groups, study outcomes, languages, or participant types.

For studies identified through PubMed and Web of Science, we manually retrieved clinical trial registration numbers by reviewing the full texts and cross-referenced them with registry entries (e.g., National Clinical Trial [NCT] identifiers from ClinicalTrial.gov). Duplicate records based on registration numbers were removed. Publications from PubMed and Web of Science that met the selection criteria but lacked corresponding registry numbers were also retained to ensure a comprehensive overview of DHT applications in rare disease trials. All included studies were manually reviewed to ensure relevance and accuracy.

Data selection and screening

This systematic review was conducted in accordance with the PRISMA 2020 guidelines, and the PRISMA checklist was followed throughout the process.

To improve efficiency and ensure screening quality, we utilized Rayyan (https://www.rayyan.ai/), an online review tool to screen articles and trials data. Records retrieved from Clinicaltrials.gov, ICTRP databases, Cochrane Library, PubMed, and Web of Science were downloaded and imported into Rayyan. Reviewers were not blinded to journals or authors during the screening process. A screening guide was developed prior to the initial screening to train all reviewers on the eligibility criteria (protocol CRD420251088025 in PROSPERO). During the first round, study titles and abstracts were independently reviewed by two reviewers (XM and XW) using the Rayyan platform. Records that met the inclusion criteria proceeded to a second round, during which full-text screening was conducted by the same reviewers. Discrepancies between the two reviewers were resolved through discussion and consensus, with a third reviewer (DZ) involved when necessary. Reasons for exclusion during full-text review were documented.

Extraction and classification of DHTs using GPT-4.0

The increasing application of digital technology in clinical trials necessitates systematic classification to map application scenarios accurately. To support this process, we employed the Generative Pretrained Transformer model (GPT-4.0), developed by OpenAI, to extract and categorize unstructured information from clinical trial records. GPT-4.0's advanced semantic understanding capabilities allowed for initial identification and categorization of DHTs used in the included studies. The process began with GPT-4.0 performing a preliminary screening of study titles and abstracts, extracting and classifying digital technologies into broad functional domains (Supplementary Data 1). To ensure consistency and precision, all classifications were meticulously reviewed, and refined by domain experts. Any discrepancies or misclassifications were corrected through manual verification to uphold methodological rigor. The final classification framework included six primary categories corresponding to clinical study processes: patient recruitment, digital treatment, data monitoring and collection, outcome assessment, remote follow-up, and long-term care management. Within the digital treatment domain, further subcategories—such as digital cognitive therapy, digital physiotherapy, mental health therapy and palliative care—were initially generated with GPT-4.0 assistance and finalized through expert validation to ensure clarity and consistency.

Clinical study characteristics

All included studies were categorized based on key characteristics, including study duration, start year, geographical location and the number of clinical centers involved. Duration was calculated as the time (in years) between the reported start and end dates. Geographical distribution was defined by the countries or regions where the studies were conducted. Studies were classified as single-center or multi-center based on the number of trial sites involved. Additionally, trials were grouped by participant enrollment size and demographic characteristics (e.g., age groups) to better understand the scale and population diversity of the studies. Since clinical trial registries rely on sponsor-reported information, analyses were conducted using only available data.

Statistics and reproducibility

Descriptive statistics included proportions for categorical variables and using medians and interquartile ranges (IQRs) for continuous variables. All analyses were performed using R (version 4.3.0), with p-values less than 0.05 considered statistically significant.

To assess the DHT adoption rate in rare disease clinical trials, we conducted a targeted search on ClinicalTrials.gov for all interventional trials related to the ten selected rare diseases, starting from 2017—the first year in which more than ten DHT-enabled trials appeared in our dataset. For each disease, the total number of trials identified served as the denominator. and the number of previously identified DHT-enabled trials served as the numerator. The adoption rate was calculated separately for each disease. To explore temporal trends, we stratified the data into two periods—2017–2020 and 2021–2024—corresponding to the pre- and post-pandemic eras.

Results

Using 53 search terms related to digital health and the ten selected rare diseases (see Supplementary Table 1), a total of 8373 clinical trial records and publications were initially retrieved from Clinicaltrials.gov, the ICTRP, Cochrane, PubMed and Web of Science. Following title and abstract screening for relevance to digital technologies and the diseases of interest (Fig. 1), 470 records were selected for full-text assessment. Of these, 166 were excluded due to a lack of direct relevance to DHTs or to the target rare diseases, and 42 records were removed as duplicates based on trial registry numbers. Ultimately, 262 studies were included in the final analysis. Among these, 183 trials were registered on ClinicalTrial.gov, 56 were identified from other trial registries such as the ICTRP and Australian New Zealand Clinical Trials Registry (ANZCTR), and 23 were standalone publications not linked to any available registration.

All included studies were classified into six distinct domains: patient recruitment, digital treatment, data monitoring and collection, outcome assessment, remote follow-up, and long-term care management. Trials involving digital treatments were further subdivided into six modalities (Fig. 1) based on therapeutic focus and technological modality.

Year trends in the use of DHTs

The use of DHTs in interventional trials for the selected rare diseases first appeared in 2009 and showed a gradual but consistent increase through 2019 (Fig. 2). A marked surge was observed in 2020 and 2021, likely driven by the urgent need for remote and decentralized trial operations in response to logistical challenges imposed by the COVID-19 pandemic[12,15]. Another notable uptick occurred in 2024, with 44 trials initiated in the first half of the year alone, indicating sustained momentum in DHT adoption. This continued growth may reflect the recognized benefits of digital tools, such as streamlined data collection[16] and improved patient engagement[17]. Regarding study status, 120 studies (45.8%) were reported as completed, with a median study duration of 2.0 years (IQR 0.93–2.82). An additional 42 (16.0%) were actively recruiting at the time of analysis.

Use of DHTs in clinical trials by rare disease

Among the ten rare diseases analyzed, DHTs were most frequently applied in clinical trials for CF, accounting for 102 trials (38.9%) out of the 262 included. This was followed by 42 trials for ALS, 26 for PH, 20 for FTD and 19 for PF (Supplementary Fig. 1). To calculate the proportion of trials employing digital technologies, supplementary searches were performed on ClinicalTrials.gov to identify all interventional trials related to each rare disease, with these totals serving as denominators.

To evaluate changes in DHT adoption over time, data were stratified into two periods—2017–2020 and 2021–2024. Across these periods, most of the selected diseases showed increased adoption (Fig. 3). The largest increases were recorded in trials for CF, FTD and ALS, with respective rises of 15.7%, 13.1% and 10.8%. These three diseases also ranked among the top four in both the absolute number and relative proportions of DHT-utilizing trials during the 2021–2024 period (Supplementary Fig. 1). These conditions share key characteristics—they are relatively chronic, progressive, and require continuous monitoring and personalized care—making them especially well-suited to DHT-enabled approaches. The most frequently used technologies in these trials were data monitoring and collection, and long-term care management (Table 1), both of which align closely with the monitoring and support needs of these patient populations. Additionally, DMD and HD exhibited relatively high proportions of DHT uptake (Fig. 3), with digital treatment being the most prominent application (Table 1). This likely reflects the need for rehabilitation strategies tailored to disease-specific challenges: DMD requires interventions aimed at preserving motor function[18], and HD may benefit from cognitive and behavioral therapies that addressing motor impairments and neurocognitive decline[19]. By contrast, acute-onset conditions such as ARDS, GVHD, and CRS showed relative low

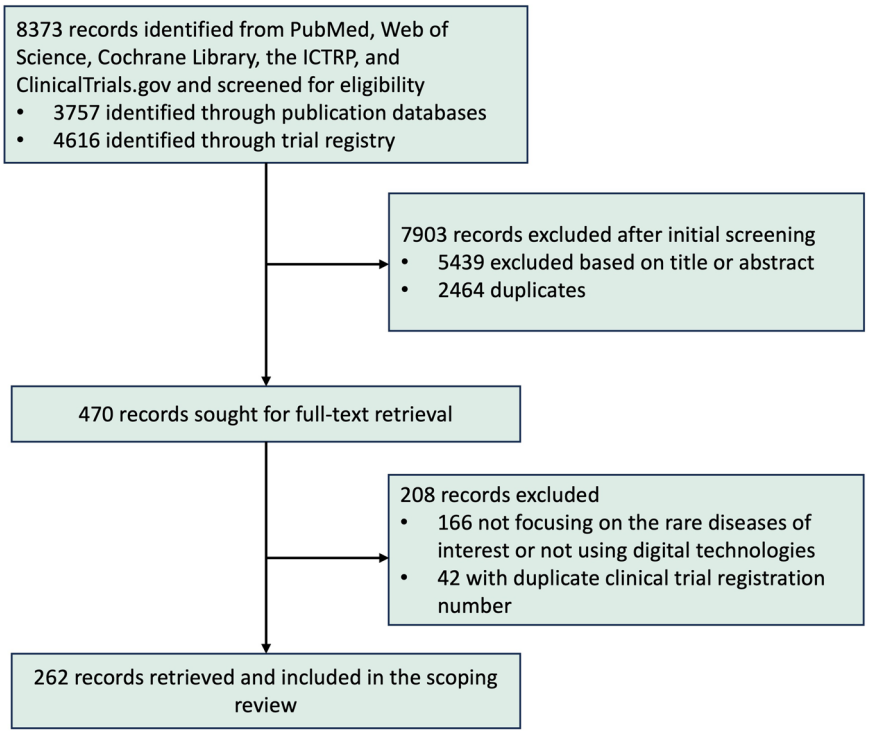


Fig. 1 | PRISMA study diagram. A total of 8373 records were identified through database and trial registry searches. After title/abstract screening and removal of duplicates, 470 full-text articles were assessed for eligibility, resulting in 262 studies included in the final scoping review. Included studies were categorized according to their digital health application scenarios (e.g., recruitment, digital treatment, long-term care), and further classified into specific therapy types such as digital cognitive therapy, virtual reality therapy, and palliative therapy.

levels of DHT utilization both in numbers and in proportion terms. This may be attributed to their rapidly progressing clinical courses, which often require immediate and intensive in-person care, rendering remote or digital interventions less applicable.

Functions of DHTs in rare disease trials

To further elucidate the specific roles of DHTs, we employed ChatGPT 4.0, supplemented by expert manual verification, to categorize these technologies into six major domains, each corresponding to distinct stages of clinical trial process. Among these, data monitoring and collection emerged as the most prevalent application, featuring in 82 clinical trials and representing 31.3% of all included studies (Table 2). Digital treatment ranked second, applied in 57 trials (21.8%), followed by long-term care management in 54 trials (20.6%). Other domains included remote follow-up (46 trials, 17.6%), outcome assessment (18 trials, 6.9%), and recruitment (5 trials, 1.9%).

In the domain of patient recruitment, five studies reported adopting digital methods to address challenges in participant enrollment and randomization management. One study [NCT05444244] implemented an online recruitment strategy based on a community registry, successfully enrolling 182 participants with dementia, including those with FTD, within 10 months—a stark contrast to the zero participants recruited through traditional methods. The other four studies leveraged electronic health record (EHR)-based algorithms to identify eligible patients or employed web-based randomization systems to streamline recruitment and allocation.

For data monitoring and collection, home monitoring systems were the most frequently used technologies, documented in 22 (26.8%) clinical trials. Wearable devices, applied in 17 (20.7%) trials, enabled continuous monitoring of physiological functions, such as cardiopulmonary performance, in routine home settings. For instance, one study [NCT01027884] employed weekly home-based spirometry to monitor pulmonary function in patients with DMD[20]. Another [NCT03104322] deployed a digital platform for IPF to track symptom progression. Additionally, the study [NCT03420235] implemented a home monitoring program that tracked symptoms, medication use, and lung functions to improve disease-specific health-related quality of life (HRQoL) in patients with IPF. Patients reported high acceptability of these tools, citing increased convenience and enabled personalized tracking of symptoms and treatment responses[21].

The 57 studies in the domain of digital treatment were categorized into six subgroups based on therapeutic modality. Digital physiotherapy was the most prevalent (25 trials, 43.9%), providing support for rehabilitation and functional recovery. Digital cognitive therapy was employed in 9 trials (15.8%) across five diseases. Digital game therapy and virtual reality therapy were tested in 8 (14.0%) and 7 trials (12.3%), respectively, aimed at improving patient engagement, motor functions and rehabilitation outcomes. Mental health therapy, featured in 4 trials (7.0%), focused on improving emotional well-being. Palliative therapy in another 4 trials, sought to alleviate disease-related pain and improve quality of life (QoL). The diverse set of digital interventions demonstrates strong potential for functional improvement and symptom relief, which is particularly valuable in rare diseases where effective therapies remain limited.

Among 46 studies in the remote follow-up domain, 43 trials (93.5%) utilized synchronous tools, such as video calls and remote counseling, to provide clinical guidance where in-person visits were not feasible. Three additional studies applied online surveys and questionnaires to gather patient-reported data remotely, supporting aspects of follow-up in decentralized settings. For long-term care management, 70.3% (38/54) of the studies focused on patient self-management, primarily through mobile applications supporting dietary tracking and vital sign monitoring. The remaining 16 trials (29.7%) targeted healthcare providers, providing digital education and training resources to enhance clinical knowledge and procedural familiarity. In terms of outcome assessment, 18 (6.8%) studies applied DHTs to facilitate timely evaluation of therapeutic interventions, including patient-reported outcomes and digitally captured functional measures. These tools supported remote, standardized assessment of clinical benefit, particularly in decentralized trial settings.

Characteristics of included studies

Among the included trials, 119 (45.4%) were randomized controlled trials (RCTs) and the majority (80.5%) focused on adult populations. Sample sizes were generally small (median: 48, IQR 25–94), reflecting both the rarity of the diseases studied and the exploratory nature of early-stage research. Specifically, 132 trials (50.3%) enrolled fewer than 50 participants, and 56 trials (21.3%) had sample sizes between 50 and 100 (Supplementary Fig. 2). Larger-scale trials were less common: 31 trials planned to recruit over 200

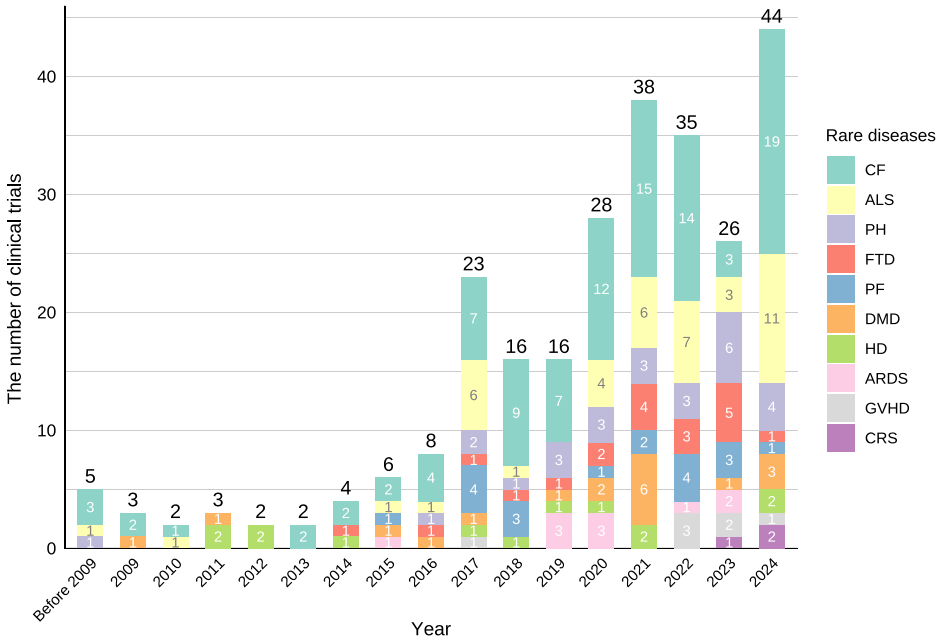


Fig. 2 | Annual number of interventional trials using DHTs in selected rare diseases. Data for 2024 includes trials registered up to June 26. Note: ALS amyotrophic lateral sclerosis, PF pulmonary fibrosis, ARDS acute respiratory distress syndrome, DMD Duchenne muscular dystrophy, CF cystic fibrosis, HD Huntington's disease, PH pulmonary hypertension, CRS cytokine release syndrome, FTD frontotemporal dementia, GVHD graft-versus-host disease.

participants, including three exceeding 1000. These three trials included a broader disease spectrum, with rare diseases represented as subgroups. One such trial [NCT05669365] aimed to recruit 2550 individuals with dementia and their caregivers, including a subset with FTD. Regarding intended users of DHTs, most applications (91.2%) was patient-facing, with 15 trials (5.6%) targeting healthcare providers and 8 trials (3.0%) involving both user groups.

Geographically, 234 trials reported study locations across more than 20 countries. The United States had the highest number of DHT-enabled trials (92, 39.3%), followed by the United Kingdom (15.0%), France (8.1%), and Australia (5.1%), while China accounted for only three trials (1.3%) (Supplementary Fig. 3). Among the 220 trials with available site information, 157 (71.4%) were single-center trials, and 63 (28.6%) were multi-center trials, including seven international trials.

Analysis of completed DHT-enabled trials

Among the 262 included studies, 56 studies (21.4%) had publicly available results. Of these, 26 directly evaluated the effects of digital treatment interventions. As summarized in Supplementary Data 2, the majority of these comparative studies reported favorable outcomes associated with digital interventions. For instance, Del Corral et al.[22] conducted a RCT in Spain to assess the effect of a home-based exercise game program using the Nintendo Wii™ platform in patients with CF. The intervention group experienced a significant improvement in walking capacity compared to the control group ($p < 0.05$). Another multicenter RCT in Belgium[23] demonstrated that use of eGVHD App significantly improved diagnostic accuracy and scoring consistency compared to standard clinical assessment ($p < 0.001$).

Discussion

Over the past few decades, substantial global efforts have been undertaken to advance therapeutic development for rare diseases through supportive regulatory policies and economic incentives[24,25]. In the US, landmark initiatives such as the Orphan Drug Act (1983)[26] and the Accelerating Rare disease Cures program (2022) have promoted this mission by driving scientific innovation, regulatory flexibility and stakeholder engagement[27]. Likewise, the European Medicines Agency (EMA) has introduced a suite of incentives, including market exclusivity, fee reductions, and scientific advice, to stimulate orphan drug development. In China, supportive policies like accelerated approval pathways for urgently needed orphan drugs (UNOD) and Care for Rare Diseases Encouragement (CARE) plan[28], have been implemented to improve access to therapies for rare conditions. Despite these advances, approved treatments remain available for only 5~7% of the estimated 7000 to 10,000 rare diseases worldwide[29]. Clinical trials represent the most resource-intensive and failure-prone phase of drug R&D—and are even more complex in the context of rare diseases (Table 1). Small, geographically dispersed patient populations and high phenotypic variability often lead to slow recruitment, limited statistical power, and extended trial durations[30–34]. Addressing these challenges is critical to advancing robust and inclusive therapeutic research for underserved populations.

Our study highlights a significant upward trend in the deployment of DHTs in interventional trials for selected rare diseases, particularly since 2020 (Fig. 3). To capture the most recent developments, we conducted a supplementary search extending through the end of 2024, identifying nearly 60 additional DHT-enabled rare disease trials initiated in that year alone. Returning to our primary dataset, we found that in certain conditions such as CF and FTD, over 20% of recent trials incorporated digital components—a proportion higher than the reported 11% adoption rate in trials for common neurological disorders in 2020[35]. These findings raise important questions about what makes digital technologies increasingly valuable in the rare disease trial landscape, and what benefits they offer beyond logistical convenience.

DHTs enhance trial accessibility by enabling remote participation, thereby mitigating recruitment delays caused by small, scattered populations. For instance, telemedicine platforms such as Amwell and Teladoc Health enable remote consultation with specialists, and eConsent platforms like Medidata eConsent and REDCap streamline informed consent processes and reduce in-person requirements. Beyond accessibility, DHTs also enhance operational agility by simplifying workflows and providing more patient-friendly options. Wearable biosensors (e.g., ActiGraph, Biofourmis) and mobile health (mHealth) applications (e.g., Apple ResearchKit, Google Fit) support real-time home-based monitoring of vital signs, medication adherence, and disease progression. Electronic clinical outcome assessment (eCOA) platforms, such as Medable and Clinical Ink, enable patients to report symptoms and QoL metrics in a timely and structured manner.

In addition to improving accessibility and agility, DHTs also hold promising potential to improve therapeutic outcomes in rare diseases. Our analysis of controlled studies with available results highlights the feasibility and benefits of various digital therapeutic and long-term care interventions

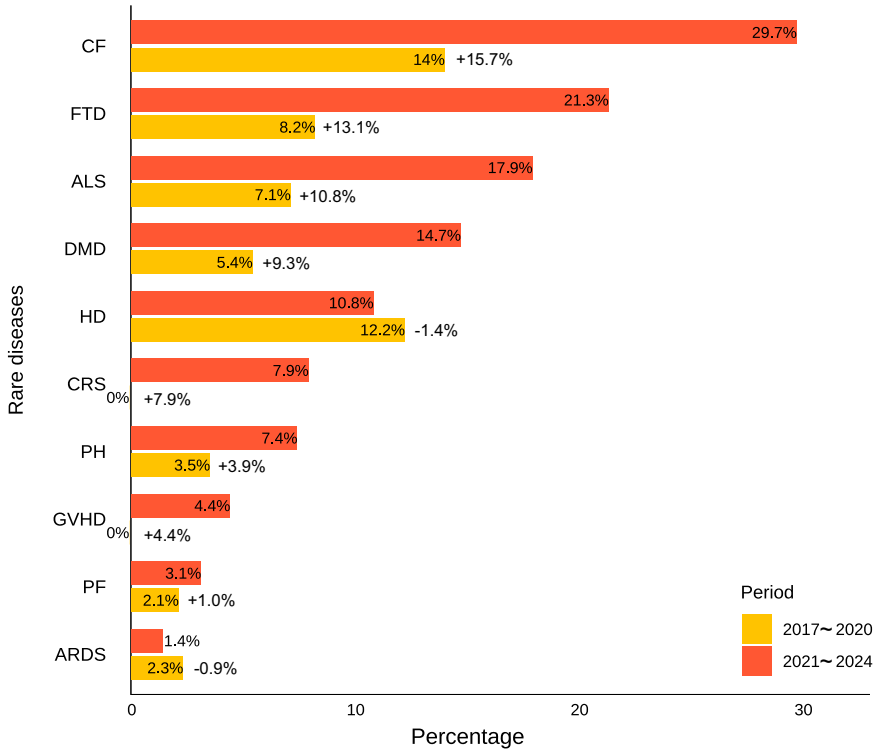


Fig. 3 | Changes in the proportion of clinical trials using of digital technologies across selected rare diseases between 2017–2020 and 2021–2024. Data for 2024 includes trials registered up to June 26. Note: ALS amyotrophic lateral sclerosis, PF pulmonary fibrosis, ARDS acute respiratory distress syndrome, DMD Duchenne muscular dystrophy, CF cystic fibrosis, HD Huntington's disease, PH pulmonary hypertension, CRS cytokine release syndrome, FTD frontotemporal dementia, GVHD graft-versus-host disease.

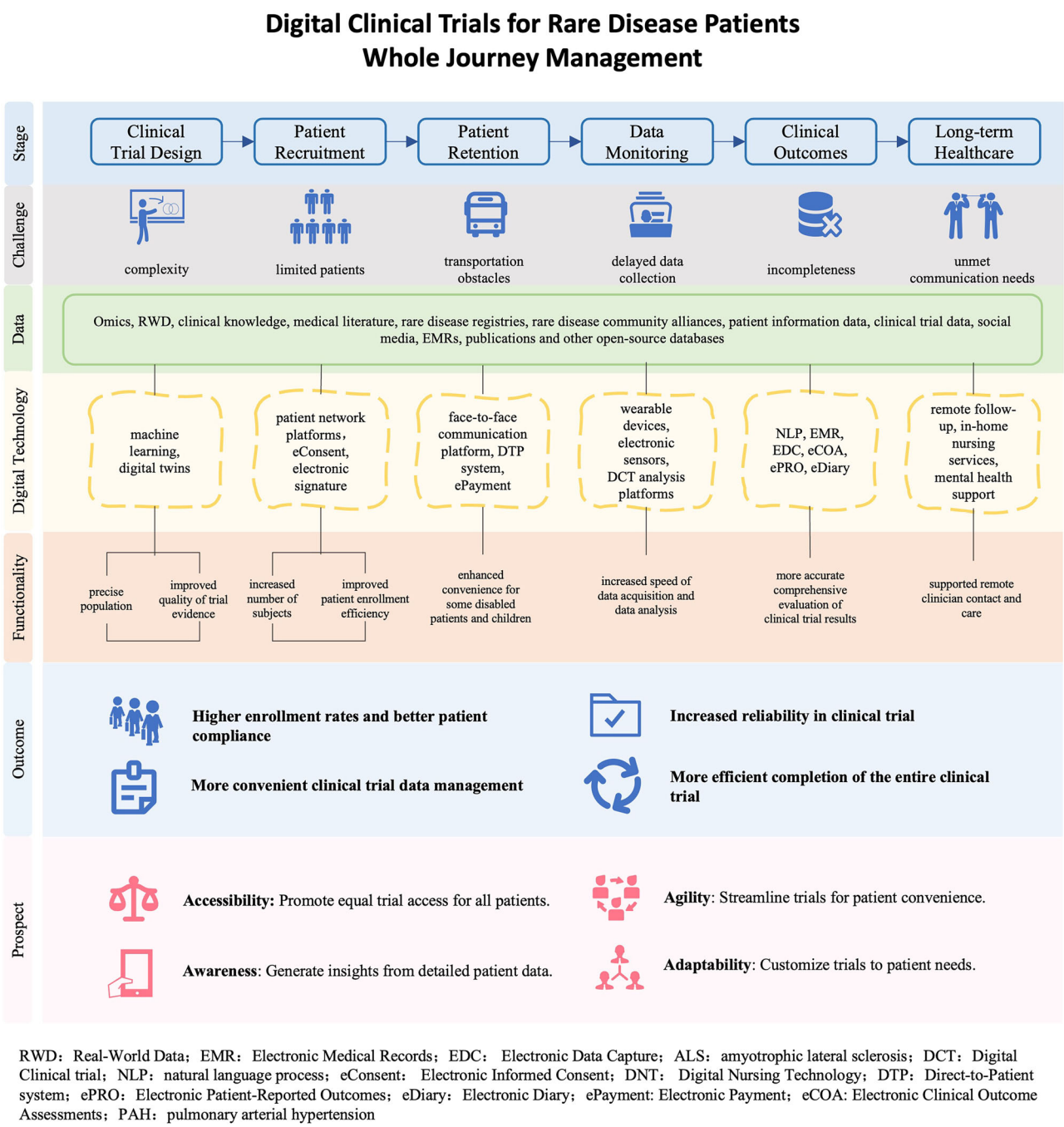
Table 2 | The classification of DHTs utilized in clinical trials for rare diseases

	Recruitment	Digital treatment	Data monitoring and collection	Remote follow-up	Outcome assessment	Long-term care management	All
ALS	0	7 (16.67%)	17 (40.48%)	6 (14.29%)	4 (9.52%)	8 (19.05%)	42
ARDS	1 (10.00%)	3 (30.00%)	1 (10.00%)	2 (20.00%)	0	3 (30.00%)	10
CF	2 (1.96%)	15 (14.71%)	33 (32.35%)	24 (23.53%)	4 (3.92%)	24 (23.53%)	102
CRS	0	0	3 (100%)	0	0	0	3
DMD	0	7 (38.89%)	6 (33.33%)	4 (22.22%)	0	1 (5.56%)	18
FTD	2 (10.00%)	4 (20.00%)	2 (10.00%)	3 (15.00%)	1 (5.00%)	8 (40.00%)	20
GVHD	0	1 (14.29%)	2 (28.57%)	1 (14.29%)	2 (28.57%)	1 (14.29%)	7
HD	0	8 (57.14%)	2 (14.29%)	0	2 (14.29%)	2 (14.29%)	14
PF	0	5 (26.32%)	8 (42.11%)	2 (10.53%)	2 (10.53%)	2 (10.53%)	19
PH	0	7 (25.93%)	8 (29.63%)	4 (14.81%)	3 (11.11%)	5 (18.52%)	27
All	5 (1.91%)	57 (21.76%)	82 (31.3%)	46 (17.56%)	18 (6.87%)	54 (20.61%)	262

ALS amyotrophic lateral sclerosis, *PF* pulmonary fibrosis, *ARDS* acute respiratory distress syndrome, *DMD* Duchenne muscular dystrophy, *CF* cystic fibrosis, *HD* Huntington's disease, *PH* pulmonary hypertension, *CRS* cytokine release syndrome, *FTD* frontotemporal dementia, *GVHD* graft-versus-host disease.

(Supplementary Data 2), particularly in symptom relief and QoL improvements. For example, an automated text message based intervention successfully increased physical activity in patients with PAH[36] ($p = 0.02$). A home-based programme using active video games effectively improved exercise capacity, muscular strength and short-term QoL in children and adolescents with CF ($p < 0.05$)[22]. However, conducting a meta-analysis across studies remains challenging due to heterogeneity in disease characteristics, clinical outcomes, and evaluation metrics. Nonetheless, the available evidence underscores the clinical relevance and future promise of DHTs in supporting care for rare disease populations.

Current applications of DHTs are predominantly concentrated in four domains: digital treatment, data monitoring and collection, long-term healthcare and remote follow-up (Table 2). Despite the transformative potential of DHTs, their effective implementation requires alignment with the specific clinical contexts and needs of each disease. This is reflected in our findings, which reveal marked variation in DHT adoption across the selected diseases. For instance, CF trials exhibited the highest level of digital utilization across multiple domains, owing to its complex and chronic nature, which necessitates continuous monitoring, long-term care management, and proactive intervention to maintain lung function and prevent exacerbations[37]. ALS studies showed substantial use of data monitoring technologies, reflecting the critical need to track rapid disease progression and manage associated symptoms. These patterns underscore the importance of tailoring DHT strategies to disease-specific characteristics to maximize their clinical relevance and impact.



RWD：Real-World Data；EMR：Electronic Medical Records；EDC： Electronic Data Capture；ALS：amyotrophic lateral sclerosis；DCT：Digital Clinical trial；NLP：natural language process；eConsent： Electronic Informed Consent；DNT： Digital Nursing Technology；DTP：Direct-to-Patient system；ePRO：Electronic Patient-Reported Outcomes；eDiary：Electronic Diary；ePayment: Electronic Payment；eCOA: Electronic Clinical Outcome Assessments；PAH：pulmonary arterial hypertension

Fig. 4 | The end-to-end DHT applications in rare disease clinical trials. This framework illustrates how DHTs can address specific challenges throughout the clinical trial continuum—from trial design, patient recruitment, retention, and monitoring, to outcome evaluation and long-term healthcare. It maps available data types, relevant digital tools, and their functionalities, highlighting how DHTs enhance patient access, operational efficiency, and trial robustness. The "4A" prospect—Accessibility, Agility, Awareness, and Adaptability—summarizes the broader value of DHTs for rare disease research.

Across the entire rare disease trial continuum, DHTs hold promise to support patient-centric approaches—from trial design to patient recruitment and retention, and to data monitoring, outcome assessment, and long-term healthcare (Fig. 4). However, as our analysis primarily draws from trial registries and published literature, it may not fully capture the breadth or depth of DHT integration across all stages of clinical research. Additionally, given the existence of over 10,000 rare diseases, and especially the scarcity of research on ultra-rare conditions, capturing the full landscape remains inherently challenging. To complement this view, we conducted supplementary searches on Google Scholar and grey literature, aiming to provide a broader, though non-exhaustive, picture of DHT applications beyond formal trial registries and publications.

During the trial design phase, digital approaches such as machine learning algorithms and digital twin models enable precise cohort selection and the generation of predictive models to optimize sample sizes—an essential feature for rare diseases with limited patient pools. Platforms like TwinRCTs™[38], Clinerion[39], and Deep 6 AI[40] have been leveraged to support more data-driven, patient-tailored trial designs[41]. In the recruitment phase, digital platforms broaden patient outreach and improve enrollment efficiency[7]. Patient network systems such as the US National Institutes of Health's Rare Diseases Clinical Research Network[42] and the National Rare Diseases Registry System of China[43] facilitate access to geographically dispersed populations. To support patient retention, direct-to-patient (DTP) drug delivery systems and digital communication platforms ease logistics

and improve compliance, particularly for patients with continuous care needs or with mobility limitations. Digital treatment modalities, such as mental health therapies and game-based interventions, offer the psychological support and engagement particularly suited to pediatric rare disease patients[44,45]. Home-based physiological monitoring using wearable devices and mobile apps is also becoming more widespread[46]. Beyond data acquisition, platforms such as Medidata cloud platform[47], Veeva Systems[48] and Oracle Health Sciences[49] provide integrated infrastructure for real-time data processing, disease monitoring and outcome assessment. In the context of long-term healthcare, DHTs help bridge persistent communication gaps between patients and healthcare providers. They support remote consultations, in-home nursing services and online training programs, collectively contributing to improved QoL for patients[50]. Together, these tools illustrate how DHTs can be strategically applied across trial stages to address challenges specific to rare disease populations.

Looking ahead, to better navigate and consolidate the complex landscape of DHT applications in rare disease research, we propose an integrated framework (Fig. 4) that maps digital tools onto six key stages of the trial process: from trial design to long-term healthcare. This framework outlines stage-specific challenges, identifies applicable data types and digital technologies, highlights how DHTs can improve trial efficiency, data quality, and patient engagement. Building on this structure, we recommend that future DHT deployment can be guided by four foundational principles—Accessibility, Agility, Awareness, and Adaptability ("4A"). These principles provide a strategic lens to ensure more inclusive, efficient, and patient-centered research.

Accessibility ensures that patients with rare diseases have equitable opportunities to engage in research through remote access and decentralized trial model[30,51]. Agility emphasizes streamlined trial operations to reduce logistical burdens, enabling seamlessly participation through wearable devices, home-based monitoring systems, and virtual consultations—particularly beneficial for those managing chronic and progressive conditions. Awareness underscores the value of real-world data, and patient-reported outcomes in deepening understanding of rare disease biology, progression, and patient needs—filling knowledge gaps that often hinder therapeutic progress. Adaptability reflects the need to tailor studies to the evolving needs of rare disease populations, where the focus extends beyond survival to improving QoL and ensuring patients can live with greater dignity.

As technology continues to evolve and regulatory frameworks adapt, the adoption of DHTs in rare disease clinical trials is poised to expand further. Numerous emerging DHTs, such as next-generation wearable devices, large language models[52], and digital twins[53], are expected to revolutionize clinical trial paradigm[54]. For instance, medical digital twins —computational models that replicates human biology relevant to a compound or intervention—are gaining traction in medical research[55]. These advancements herald a shift towards virtual clinical trials[56], which provide an efficient and scalable alternative for rare diseases with limited patient pools. Meanwhile, large language model (LLM) technologies are reshaping conventional clinical development processes, facilitating patient matching[57,58], protocol design[59], and early prediction of trial outcomes[60].

However, despite their transformative potential, DHTs in clinical trials still face multifaceted challenges[61]. Firstly, safeguarding patient data remains paramount. This requires robust data governance frameworks, end-to-end encryption, and secure, interoperable data hubs[62] to ensure compliance with The Health Insurance Portability and Accountability Act of 1996 (HIPAA), The General Data Protection Regulation (GDPR), and other regional regulations. Secondly, ensuring data quality and operational efficiency requires the integration of advanced management systems with real-time monitoring, AI-driven analytics, and standardized data formats. However, differences in device calibration, data transmission, and software compatibility pose significant challenges for seamless data integration. Adopting standards such as Fast Healthcare Interoperability Resources (FHIR) and Clinical Data Interchange Standards Consortium (CDISC), along with automated validation tools, can facilitate data harmonization and interoperability across platforms. Third, integrating AI into clinical trials raises ethical concerns, including algorithmic bias, lack of explainability of decision-making, and risks of hallucinations or misdiagnoses that could negatively impact patient outcomes. These issues necessitate the development of dedicated ethical and regulatory frameworks. Fourth, ensuring digital equity remains a critical concern[30]. Unequal access to digital devices and reliable internet connectivity, particularly in low- and middle-income countries (LMICs), impedes participation in digital trials. Socioeconomic disparities, limited digital literacy, and language barriers further exacerbate exclusion. To address the language gap for First Nations people, the DHT-enabled Lyfe Languages platform, which initially launched a rare disease module, plans to expand its translations and educational resources into additional domains such as clinical trials and treatment information. Beyond infrastructure limitations, certain patient populations, such as the elderly and individuals with physical or cognitive impairments, may face difficulties in interacting with wearable devices and telemedicine platforms. Addressing these disparities requires efforts to enhance accessibility, strengthen infrastructure, and design inclusive digital solutions. Ensuring equitable participation is essential to maximizing the impact of DHTs in clinical research[63,64].

This study has several limitations. First, the historical absence of a globally unified definition of rare diseases constrained our study scope to the top ten rare diseases with the highest R&D activity, which may not fully represent the broader spectrum of rare disease research. This approach inevitably excludes some less-studied conditions, particularly those with very small patient populations or those that have only recently been the focus of pharmaceutical interest, but it nonetheless captures the lion's share of DHT investment and innovation in the rare disease space. Indeed, as of 2024, the 10th-ranked disease, GVHD, had only seven DHT-enabled trials, suggesting that this focus is sufficient to capture key trends. Second, the application of DHTs is often underreported or undocumented, making it difficult to assess their full usage. To mitigate this, we conducted supplementary searches and developed an end-to-end "4A" application framework to provide a more comprehensive perspective.

In conclusion, this study reveals a growing trend in the integration of DHTs into patient-centric clinical trials for rare diseases, particularly in digital therapeutics, data monitoring and long-term care management. By enabling more inclusive, efficient, and tailored trial designs, these technologies pave the way for a paradigm shift in rare disease research. Beyond mapping current use cases, we propose a forward-looking framework centered on four key principles—Accessibility, Agility, Awareness, and Adaptability—to guide the meaningful application of DHTs. As technological innovations and supportive policies evolve, DHTs hold immense potential to redefine clinical research, creating a future where rare disease patients have equitable access to effective therapies and improved health outcomes. We call on researchers and policymakers to embrace the 4A framework and strengthen cross-sector collaboration, ensuring that DHTs reach their full potential in improving rare disease research and patient care.

Data availability

A total of 262 studies analyzed in this study were identified through ClinicalTrials.gov, the International Clinical Trials Registry Platform, Cochrane Central Register of Controlled Trials, PubMed, and Web of Science. All data used for the analyses were extracted from published studies and are included in the Article. And all specific data and list included in this study are available from the corresponding author on reasonable request.

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Author contributions

X.M. and D.Z. planned and drafted the paper, and contributed to data quality control, analysis, and interpretation. T.Y.W., G.L., and S.Z. led the overall planning and data interpretation. X.W. contributed to data quality control and interpretation. D.A.P., G.B., N.H.C., W.K.C., H.W., and Y.C.T. provided methodological guidance and support with data interpretation. All authors reviewed and revised the manuscript.

Competing interests

T.W. is the deputy group chief executive officer (research and education) of Singapore Health Services, a consultant & advisory board for Allergan, Bayer, Boehringer-Ingelheim, Genentech, Merck, Novartis, Oxurion (formerly ThromboGenics), Roche, and co-founder of plano and EyRiS. The remaining authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Shuyang Zhang, Guanqiao Li or Tien Yin Wong.

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[1]Vanke School of Public Health, Tsinghua University, Beijing, China. [2]Institute for Healthy China, Tsinghua University, Beijing, China. [3]Tsinghua Medicine, Tsinghua University, Beijing, China. [4]Department of Pediatrics, Sanford School of Medicine, University of South Dakota, Sioux Falls, SD, USA. [5]International Rare Disease Research Consortium, Paris, France. [6]Rare Care Centre, Perth Children's Hospital, Perth, WA, Australia. [7]Western Australian Register of Developmental Anomalies, King Edward Memorial Hospital, Perth, WA, Australia. [8]Faculty of Health and Medical Sciences, University of Western Australia, Perth, WA, Australia. [9]School of Medicine and Psychology, Australian National University, Canberra, Australia. [10]Department of Public Health and Primary Care, National eHealth Living Lab, Leiden University Medical Center, Leiden, The Netherlands. [11]Department of Pediatrics, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA. [12]Institute of Health Informatics, University College London, London, United Kingdom. [13]School of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom. [14]Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore. [15]Centre for Innovation and Precision Eye Health, Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore, Singapore. [16]Singapore Eye Research Institute, Singapore National Eye Centre, Singapore, Singapore. [17]Ophthalmology and Visual Science Academic Clinical Program (Eye ACP), Duke-NUS Medical School, Singapore, Singapore. [18]State Key Laboratory of Complex Severe and Rare Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China. [19]Department of Cardiology, Peking Union Medical College Hospital, Beijing, China. [20]School of Clinical Medicine, Tsinghua Medicine, Tsinghua University, Beijing, China. [21]Beijing Key Laboratory of Intelligent Diagnostic Technology and Devices for Major Blinding Eye Diseases, Tsinghua Medicine, Tsinghua University, Beijing, China. [22]Beijing Visual Science and Translational Eye Research Institute (BERI), Beijing Tsinghua Changgung Hospital Eye Center, Tsinghua Medicine, Tsinghua University, Beijing, China. [23]These authors contributed equally: Xiangyun Mao, Dian Zeng. ✉e-mail: shuyangzhang103@nrdrs.org; guanqiaoli@tsinghua.edu.cn; ophwty@nus.edu.sg