INNOVATIONS IN DIGITAL THERAPEUTICS: AN ANALYSIS OF CLINICAL TRIALS AND REGULATORY STATUS IN EUROPE AND THE US

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BACKGROUND

- Digital health is an umbrella term that encompasses a variety of terms, including e-health, m-health and telehealth and captures everything from electronic patient records, remote monitoring, connected devices, digital therapeutics (DTx) and more. [1]
- DTx are innovative solutions defined by the Digital Therapeutics Alliance as “evidence-based, clinically evaluated software to treat, manage, and prevent a broad spectrum of diseases and disorders. They can be used as a monotherapy or in combination with other therapies including medications or devices to improve outcomes.” [2]
- Unlike other digital health solutions, DTx require clinically validated efficacy and regulatory approval as they are generally considered as medical devices (MD) with some exceptions. [1]
- With the increasing prevalence of chronic or difficult-to-treat conditions, DTx are expected to emerge as a new generation of personalized digital treatments. [3]

OBJECTIVE

- This study aimed to summarize current trends of DTx, and to provide an overview of their characteristics, classification and regulatory framework in Europe and the United States.

METHODS

- For this study, we reviewed DTx registered clinical trials in ClinicalTrials.gov using the keyword “digital therapeutics” without any timeframe restrictions (cut-off date: June 18, 2024).
- Phase 2 and phase 3 interventional clinical trials were extracted and analysed.
- DTx were screened and selected according to the Digital Therapeutics Alliance’s definition, presented above.
- Data related to study design, DTx characteristics, target audience were extracted and analysed as a first step.
- The analysis was complemented by an additional web search to enquire on the US and European regulatory status of DTx at advance development stage.

RESULTS

- A total of 122 clinical trials were retrieved and screened. Only 30 trials evaluated an intervention meeting the DTx definition criteria.

CLINICAL DEVELOPMENT STAGE

- Most studies (n=27) were phase 3 randomised trials, the remaining were phase 2 studies (n=3).
- Overall, 13 trials were ongoing, 10 were completed, 2 were terminated and 5 had an unknown status. (**Figure 1**)

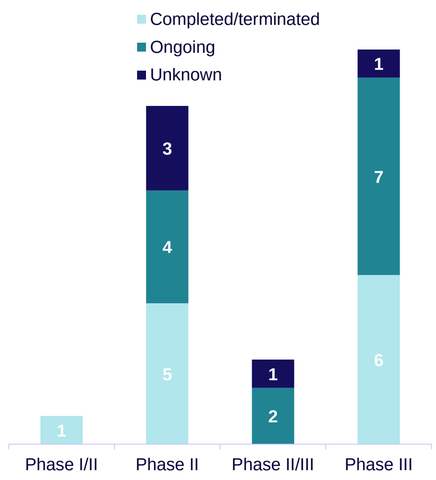

Figure 1. Distribution of identified DTx trials according to phases and status

- Most studies were conducted in the United States (US) (n=26), with fewer in Europe (n=3) and Asia (n=1).

CLASSIFICATION AND APPLICATIONS

- The objective of identified DTx was disease treatment (n=9), specific symptom management (n=13) or disease prevention (n=8).
- Most of the DTx were intended for adult patients (n=26).
- DTx solutions are being developed in several therapeutic areas covering a wide spectrum of diseases as presented in **Figure 2** mainly addiction (n=8), mental health (n=8), and neurology (n=6).
- DTx can be utilized either as standalone treatments (n=18) or in combination with conventional therapies (n=12) to enhance patient care and improve health outcomes.
- DTx are delivered through various formats, primarily mobile applications (n=24), with others including websites (n=2), virtual reality devices, digital platforms, video games, and mobile devices (n=1 each). **(Figure 3)**

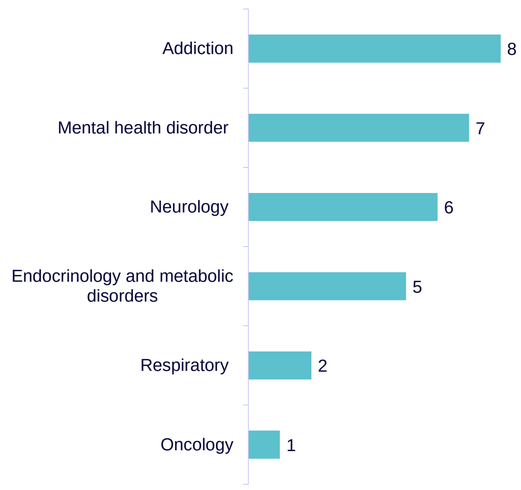

Figure 2. Distribution of identified DTx according to therapeutic areas

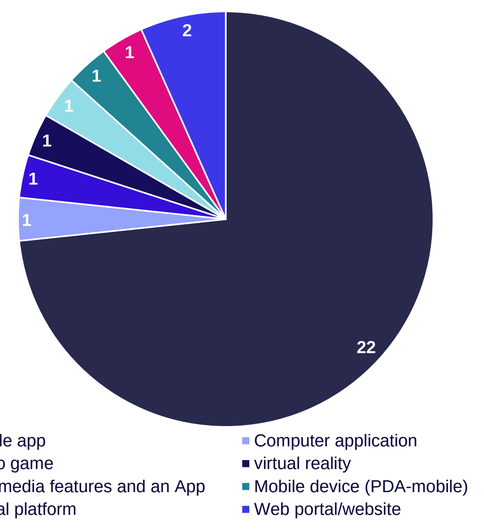

Figure 3. Distribution of identified DTx according to subtypes

REGULATORY STATUS IN THE US

- In most countries, the regulatory pathways for DTx generally align with those for MDs, though a few countries have more specialized pathways. [1]
- Although DTx are not universally classified as MDs, they are often treated as such. In both the U.S. and EU, they are classified under "Software as a Medical Device" (SaMD) or "Software in a Medical Device" (SiMD).[1]
- The Food and Drug Administration (FDA) regulates DTx under the SaMD category, recognizing distinct development and validation standards compared to hardware-based MDs. [1]
- The FDA applies to DTx a risk-based classification process that further determines the registration requirements. (**Table 1**)
- In the past 4 years, 7 of the identified DTx have received FDA approval; 3 under 510(k), and 4 through De Novo Pathway.
- Two DTx also received Breakthrough Device designation also, an MD-specific voluntary pathway that helps accelerate market approval when eligible. [1,4]

REGULATORY STATUS IN THE EU

- Unlike the US, the European Medicine Agency is not involved in DTx approval and reimbursement process. However, they are beginning to explore some solutions. [1]
- In the EU, DTx fall under MD Regulation with a risk-based classification like in the US. Depending on the risk class, they are approved by the manufacturer (Class I) or Notified Bodies (Class IIa, IIb, and III), and granted CE mark. [5]
- After obtaining CE marking, national funding criteria for DTx in Europe vary by country: effectiveness and budget impact in the UK, innovativeness in France, and medical effect in Germany, for example. [1]
- The bodies involved in these decisions are NICE in the UK, CNDiMTS in France, and BfArM under the DiGA program in Germany. [1]
- In the EU it is difficult to confirm, whether the analyzed DTx received regulatory approval. This is due to the decentralized authorization process in the EU and the limited availability of regulatory information for DTx.

Table 1. FDA risk-based assessment [1]

Class I/II (low risk)	Class II (moderate risk)	Class III (high risk)
Only general controls required: • Exemption for marketing submission but must still register and list with the FDA.	Special controls in addition to general controls. • **De Novo pathway**: Requires clinical data demonstrating the safety and effectiveness of the device • **510(k) clearance**: Must be “substantially equivalent” to a device already on the market.	• **Premarket approval application**: Requires proof of being “reasonably safe and effective” based on one premarket clinical trial and premarket inspection of manufacturing facilities.

CONCLUSIONS

- **DTx are experiencing substantial growth, with a projected 865% market increase from 2020 to 2025,[6] offering considerable opportunities for digital health and pharmaceutical companies.**
- **DTx solutions are diverse in their therapeutic applications and delivery formats, with a significant focus on chronic, behavioral, and mental health conditions where digital interventions can uniquely enhance patients’ outcomes.**
- **DTx currently follow the regulatory pathways for MDs, which may not align with their unique nature and fast-paced evolution. The absence of a dedicated DTx framework in Europe poses challenges, leading to regulatory hurdles that can slow adoption and limit patient access compared to the more flexible US system.**

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Abbreviations

AI: Artificial intelligence; **BfArM**: The federal institute for drugs and medical devices; **CE**: European conformity mark; **CNDiMTS**: national commission for evaluation of medical devices and health technologies; **DTx**: Digital therapeutics; **e-health**: electronic health; **EU**: European Union; **FDA**: Food and drugs administration; **MD**: Medical device; **m-health**: Mobile health; **NICE**: National institute of health care excellence; **PDA**: Personal digital assistant; **UK**: United Kingdom; **US**: United States