Review Article

DIGITAL HEALTH

DIGITAL HEALTH
Volume 10: 1–13

DOI: 10.1177/20552076241277703
journals.sagepub.com/home/dhj

Sage

Digital health technologies and artificial intelligence in cardiovascular clinical trials: A landscape of the European space

Fabio Lampreia[1], Catarina Madeira[1,2] and Hélder Dores[1,2,3,4]

Abstract

The recent pandemic ushered in a marked surge in the adoption of digital health technologies (DHTs), necessitating remote approaches aiming to safeguard both patient and healthcare provider well-being. These technologies encompass an array of terms, including e-health, m-health, telemedicine, wearables, sensors, smartphone apps, digital therapeutics, virtual and augmented reality, and artificial intelligence (AI). Notably, some DHTs employed in critical healthcare decisions may transition into the realm of medical devices, subjecting them to more stringent regulatory scrutiny. Consequently, it is imperative to understand the validation processes of these technologies within clinical studies. Our study summarizes an extensive examination of clinical trials focusing on cardiovascular (CV) diseases and digital health (DH) interventions, with particular attention to those incorporating elements of AI. A dataset comprising 107 eligible trials, registered on clinicaltrials.gov and International Clinical Trials Registry Platform (ICTRP) databases until 19 June 2023, forms the basis of our investigation. We focused on clinical trials employing DHTs in the European context, revealing a diverse landscape of interventions. Devices constitute the predominant category (45.8%), followed by behavioral interventions (17.8%). Within the CV domain, trials predominantly span pivotal or confirmatory phases, with a notable presence of smaller feasibility and exploratory studies. Notably, a majority of trials exhibit randomized, parallel assignment designs. When analyzing the multifaceted landscape of trial outcomes, we identified various categories such as physiological and functional measures, diagnostic accuracy, CV events and mortality, patient outcomes, quality of life, treatment adherence and effectiveness, quality of hospital processes, and usability/feasibility measures. Furthermore, we delve into a subset of 15 studies employing AI and machine learning, describing various study design features, intended purposes and the validation strategies employed. In summary, we aimed to elucidate the diverse applications, study design features, and objectives of the evolving CV-related DHT clinical trials field.

Keywords

Digital health, artificial intelligence, clinical trials, cardiovascular diseases, clinicaltrials.gov, International Clinical Trials Registry Platform

Submission date: 11 October 2023; Acceptance date: 8 August 2024

Introduction

The world health organization (WHO) has defined digital health (DH) as *the field of knowledge and practice associated with the development and use of digital health technologies to improve health. Digital health expands the concept of electronic health (eHealth) to include digital consumers, with a wider range of smart devices and connected equipment. It also encompasses other uses of digital technologies for health such as the Internet of things, artificial intelligence, big data and robotics.*[1]

[1]Associação CoLAB TRIALS, Évora, Portugal
[2]CHRC, NOVA Medical School, Lisboa, Portugal
[3]Hospital da Luz, Lisboa, Portugal
[4]NOVA Medical School, Lisboa, Portugal

Corresponding author:
Fabio Lampreia, Associação CoLAB TRIALS, Largo do Senhor da Pobreza, Escola Superior de Enfermagem São João de, Deus, Évora, 7000-811, Portugal.
Email: fabio.lampreia@colabtrials.pt

Digital health technologies (DHTs) encompass a variety of terms including e-health, m-health, telemedicine, wearables and sensors, smartphone apps, digital therapeutics, virtual and augmented reality, and artificial intelligence (AI). Such technologies aim to collect and process information from big data, electronic health records, remote monitoring activities, connected devices and more for a holistic approach to healthcare that is more inclusive of the patient in the whole process.[2,3] Some great benefits of DH have been associated with reduced inefficiencies, improved access, reduced costs, increased quality, and making medicine more personalized for patients.[4]

AI refers to techniques that allow computer systems to mimic human intelligence and behavior. Machine learning (ML), a subset of AI, uses advanced statistical techniques allowing machines to learn from data and improve with experience. AI in healthcare has emerged as a groundbreaking paradigm, leveraging sophisticated algorithms to revolutionize medical practices. In the cardiovascular (CV) space, application of AI allows the processing of vast amounts of patient data and medical literature, such as data related to diet, electrocardiogram (ECG), genetics, lifestyle, and data from various softwares and wearables or imaging data may provide insights that aid in early disease detection, personalized treatment recommendations and prognosis assessments.[5] AI promises to provide accurate diagnosis, personalized treatment plans, and predictive insights into patient outcomes. AI-powered tools, such as image recognition systems and natural language processing enhance medical imaging analysis and streamline administrative tasks, optimizing healthcare workflows.[6] Moreover, AI's ability to continuously learn and adapt empowers healthcare providers to deliver more precise, efficient, and patient-centric care. However, the integration of AI in healthcare must address ethical and regulatory considerations to ensure patient privacy, transparency, and maintain human oversight.

CV diseases are the leading cause of death globally, being responsible for almost 18 million lives every year.[7] It is therefore not surprising that novel interventions such as DHT and AI have been applied to the field with a variety of purposes. In fact, DHT research articles have been exponentially growing in the field of CV research.[8] Zwack and colleagues have described clusters of research areas in the field, such as cardiac electronic implantable devices, mobile health for secondary prevention of CV diseases, wearable technologies, stroke rehabilitation, and emergency CV care.

Some authors argue AI methods will be used in the cardiology area mainly by automating tasks that humans might otherwise perform and generating clinically relevant new knowledge for risk prediction.[9] AI in echocardiography was one of the first applications for assessment of left ventricular volume and function with automated quantification. Other relevant applications of AI in the field relate to cardiac/coronary computed tomography, automated detection of possible missing basal and apical sites in cardiac MRI, ML in nuclear cardiology to improve diagnostic accuracy and identification of perfusion defects and their location and predict early revascularization, diagnosis of heart failure (HF), interpretation of ECG and prediction of cardiac arrhythmias, the latest of which comprises on the most widespread applications.[9] Clinical trials are a foundational advancement in medical science, aiming at assessing the effectiveness and safety of novel medical interventions. Like pharmaceutical drugs, medical devices, software, and DHTs with implications in healthcare must undergo the same rigorous testing before being deployed in the wider society.[10] However, the nature of these studies can present a challenge as they can fundamentally differ from traditional pharmaceutical trials with different approaches to trial design, data collection, endpoints, ability to mask interventions, participant engagement, and trial duration and cost.

This article aims to provide a comprehensive overview of the current landscape of clinical trials involving DHTs in Europe, with a particular focus on CV diseases. By analyzing and synthesizing the existing clinical trials, we explore the various types of DHTs included in CV studies and the clinical endpoints assessed. Furthermore, we will delve into the challenges faced and opportunities presented by these trials, as well as their potential impact on patient care and clinical practice.

Material and methods

Data search

To identify relevant clinical trials, we employed the advanced search functions available on clinicaltrials.gov and ICTRP websites. Our search strategy involved utilizing specific keywords such as "digital health," "electronic health," "mobile health," "mhealth," "telehealth," "artificial intelligence," and "machine learning." On 19 June 2023, a total of 12,407 records were retrieved in CSV format, which served as the initial dataset for further analysis.

Data screening and extraction

The trials selection process was illustrated in a flowchart (Figure S1), outlining the sequential steps taken. Initially, duplicate trials were eliminated, resulting in a dataset of 11,117 records. Subsequently, trials conducted outside of Europe were excluded, narrowing down the focus. As the interest was specifically on interventional approaches, non-interventional studies were removed from the dataset. Following this, a thorough manual revision of titles and abstracts was conducted, eliminating trials unrelated to the topic of DH interventions and AI. This refining process led to the identification of 1341 relevant studies.

High-level analysis of the therapeutic areas investigated in this context was performed. To classify the health categories, an automated data mining tool utilizing the WHO classification (April 2022 version) was employed, allowing for the detection and conversion of studied conditions into ICD-11 classification categories. Non-CV disease-related trials were subsequently excluded, resulting in a final dataset of 122 records. These records underwent a comprehensive manual analysis, delving into greater detail. Further filtering steps were implemented to remove non-relevant studies, resulting in a total of 107 studies. Certain studies were excluded due to their interventions or research objectives falling outside the scope of the article. These studies encompassed a range of topics, including nutritional interventions, temperature regulation in the context of cognitive impairment post-cardiac arrest, awareness campaigns related to CV disease, feasibility assessments of prevention programs within healthcare institutions, patient interviews regarding medication adherence behaviors, provision of heart health assessments for older individuals, and observational investigations. Pertinent information, including trial registration number, title, status, conditions, interventions, outcome measures, sponsors/collaborators, gender, age, phases, enrollment, funding type, study design, time perspective, and locations, was meticulously extracted from the remaining studies.

Data processing

The primary objective of this study centered around CV-related trials, with a specific focus on extracting information pertaining to the reported outcomes. Given the extensive range of outcome types, a systematic categorization approach was employed. To facilitate this process, the primary outcomes of each study were analyzed and categorized into one of seven major outcome categories identified (physiological and functional measures, diagnostic accuracy, CV events and mortality, patient outcomes/quality of life, treatment adherence and effectiveness, quality of Hospital processes, usability and feasibility).

Statistical analysis

This study aimed to examine the features of registered trials employing DHTs, and descriptive analysis was used to analyze the variables. Only categorical variables were reported, in the form of frequencies and percentages.

Results

Characteristics of the included trials in the CV therapy area

Overview of disease areas in CV-related trials. A total of 107 trials were included (Table 1). CV-related trials represented about 9% of the records initially captured (Table S1). The most common areas in the major CV therapeutic area were HF (22.4%), cerebrovascular diseases (19.6%), ischemic heart disease (17.8%), diseases of the myocardium or cardiac chambers (12.1%), hypertensive heart disease (12.1%), arrhythmias (7.5%), symptomatic diseases of arteries or arterioles (3.7%), signs or clinical findings of the circulatory system (3.7%), and pulmonary heart disease or diseases of pulmonary circulation (0.9%) (Table S1). This is in line with the share of CV-related studies in the European clinical trial space.[11]

Characteristics of CV trials

In our analysis, we identified various types of interventions (Table 1). Devices accounted for almost half of all interventions, representing 45.8% of the total. Behavioral interventions made up 17.8%, procedures 10.3%, diagnostic tests 9.3%, and genetic tests 0.9%. Additionally, interventions that did not fit into any specific category constituted a significant portion at 20.6%.

Among the included trials, a substantial portion (39.3%) had fewer than 100 participants, suggestive of feasibility or exploratory studies. The majority (48.6%) had between 100 and 1000 participants, more typical of pivotal or confirmatory trials. A smaller fraction (10.3%) represented large trials involving over a thousand subjects. Regarding the target population, most studies (87.9%) focused on adults (18 years and older). A smaller percentage did not make distinctions based on age (7.5%), some targeted older adults specifically (3.7%), and only one study aimed both children and adults (0.9%). In terms of gender-specific trials, only two studies (1.9%) were aimed exclusively at males, while the majority (98.1%) included both males and females. As expected, medical device and DH clinical studies did not strictly adhere to traditional trial phases commonly seen in pharmaceutical trials. Specifically, we found that 93.5% of the studies did not have an applicable phase, with one study falling into phase 1 (0.9%), and three studies each fitting into phase 3 and phase 4 (2.8%) of the traditional distinctions. Regarding allocation methods, a significant proportion of trials (70.1%) were randomized, while 13.1% were non-randomized, and 15.9% did not specify their allocation approach. Concerning the intervention model, the majority (66.4%) of trials utilized a parallel assignment model. This was followed by single group assignment (18.7%), crossover (4.7%), and sequential design (2.8%). Most trials (57.9%) were open label with no masking, followed by single masking (27.1%), double masking (4.7%), triple masking (2.8%), and quadruple masking (1.9%).

When examining the primary purpose of the studies, we discovered a heterogeneous mix. The most common purpose was treatment evaluation (36.4%), followed by supportive care (16.8%), prevention (15.9%), diagnostic

Table 1. Characteristics of DHT and AI CV-related trials stratified by study design ($n = 107$).

	Percent (%)
ICD-11 codes	
Heart failure	22.4
Cerebrovascular diseases	19.6
Ischemic heart disease	17.8
Diseases of the myocardium or cardiac chambers	12.1
Hypertensive heart disease	12.1
Cardiac arrhythmia	7.5
Diseases of arteries or arterioles	3.7
Symptoms, signs or clinical findings of the circulatory system	3.7
Pulmonary heart disease or diseases of pulmonary circulation	0.9
Intervention type	
Device	45.8
Behavioral	17.8
Procedure	10.3
Diagnostic Test	4.7
Genetic	0.9
Other	20.6
Enrollment	
<100	39.3
100–1000	49.5
>1000	11.2
Age group	
Children only (<18 years)	0.0
Adults only (18–65 years)	0.0
Older adults only (>65 years)	3.7
Children and adults	0.9
Adults and older adults	87.9
All	7.5
Gender	
All	91.6
Both	6.5
Male	1.9
Phase	
Not applicable	93.5
Phase 2[a]	0.9
Phase 3[a]	2.8
Phase 4[a]	2.8
Allocation	
Randomized	70.1
Non-randomized	13.1
N/A	16.8
Intervention model	
Parallel assignment	66.4
Single group assignment	18.7
Crossover	4.7
Sequential	2.8
N/A	7.5
Masking	
Open label	57.9
Single	27.1
Double	4.7
Triple	2.8

(continued)

Table 1. Continued.

(continued)

Table 1. Continued.

	Percent (%)
Quadruple	1.9
N/A	5.6
Primary purpose	
Treatment	36.4
Supportive care	16.8
Prevention	15.9
Diagnostic	11.2
Health Services Research	9.3
Screening	0.9
Other	9.3
Top 10 countries	
Germany	16.8
United Kingdom	15.0
Spain	14.0
Sweden	14.0
Norway	7.5
Denmark	6.5
Netherlands	6.5
France	5.6
Italy	5.6
Belgium	4.7
Switzerland	4.7

[a]As per original annotation in clinical trial database.

research (11.2%), health services research (9.3%), and screening (0.9%). About 9.3% of the studies did not fall into any specific purpose category. In the subsequent sections, we will provide more detailed information about the outcomes observed in these trials.

Overview of technology applications in CV-related trials. Interventions can include devices, behavioral strategies, diagnostic tests, procedures, genetic tests, and others. We found device-related trials to incorporate telemedicine/telemonitoring systems, mobile apps, wearables, blood pressure monitors, ECG/Holter monitors, video oculography systems, AI-based tools, cardiac rehabilitation devices, and electronic health records. Behavioral interventions included feedback, lifestyle counseling, medication management, and remote health coaching. Coaching approaches have been employed to reduce CV risk factors, while cognitive behavioral therapy was shown to aid in myocardial infarction recovery. Health coaching has been a widely beneficial and recognized strategy for behavior change, both in the context of primary and secondary prevention (cardiac rehabilitation). It is a one-to-one support intervention style described as a patient-centered approach. Among the most frequent methodologies applied, motivational interviews and education sessions are common coaching interventions, delivered by telephone calls, text messages, digital-based interactions or face-to-face contacts. Several studies support the idea that health coaching can support better control CV risk factors.[12]

Lifestyle changes are emphasized for chronic ischemic heart disease, and education appears to play an important role in stroke rehabilitation and coronary artery disease (CAD). Diagnostic tests involve echocardiography for HF, AI-supported ECG interpretation, Brugada syndrome diagnosis, e-health for atrial fibrillation detection, and ML-based coronary stenosis identification. An innovative Italian study (NCT05883878) explores using digital interventions, genetic testing, and wearables to change lifestyle and CV risk profiles. Procedure-related trials mainly focus on home telemonitoring, teleconsultation, and computer-assisted diagnostic support for various conditions.

Analysis of clinical endpoints and outcomes in CV-related trials. One of the significant challenges that arises from analyzing clinical trial data is the lack of uniformity and standardization of clinical endpoints and outcomes. To address this issue, we conducted a comprehensive examination of the reported outcomes across a diverse set of CV-related trials. Our analysis identified seven major categories of outcomes, summarized in Table 2.

In summary, we observed (1) physiological and functional outcomes including changes in physical activity (like gait speed and exercise capacity), biochemical data (blood glucose, LDL-C, triglycerides), vital signs (blood pressure, oxygen consumption, heart age), dietary factors (protein consumption, diet scores), and biometric data (weight, waist circumference, hip circumference, fat mass, lean body mass, visceral fat). Scales for assessing functionality post-stroke have also been described; (2) diagnostic accuracy measures relating to the reliability of echocardiography and its impact on HF, image quality, accuracy of CAD diagnostic tests, cardiac measurements, CAD risk prediction tools, tachycardia detection, arrhythmia detection, Brugada syndrome Type 1 detection, cardiac arrest

Table 2. Primary outcome categories identified in DHT and AI CV-related trials ($n = 107$).

Primary outcome category	Percent (%)
Physiological and functional measures	29.9
Diagnostic accuracy	14.0
CV events and mortality	13.1
Patient outcomes/Quality of Life	13.1
Treatment adherence and effectiveness	11.2
Quality of Hospital processes	9.3
Usability and feasibility	9.3

recognition, improved ECG parameters, and pulmonary embolism suspicion; (3) clinical outcomes measure the impact of interventions in terms of death rates or hospitalization percentages due to any cause or CV-related events, such as HF; (4) patient-reported and quality of life outcomes focus on measuring overall quality of life and self-care behavior using scales like the hospital anxiety and depression scale, European HF self-care behavior scale, and healthcare-related quality of life EQ5DL (NCT05193344); (5) treatment adherence and effectiveness measures of various interventions (CPAP, Mediterranean diet, anti-hypertensive drugs, etc.). An example includes a digital solution for HF patients, as measured by the KCCQ-12 questionnaire; (6) quality of Hospital processes outcomes focus on improving healthcare delivery speed and quality by facilitating disease detection and treatment referencing and finally (7) usability and feasibility outcomes, often found in smaller trials, assess devices and telemonitoring approaches, measuring recruitment rates, usability by clinicians and patients, acceptability, intervention use, and user experience (NCT05330234, NCT04493437, and DRKS00014300).

Trials involving AI/ML in CV-related research. The transformative potential of AI and ML in healthcare is high, in all areas of healthcare including research, novel technologies, and methods of healthcare delivery. These technologies possess the ability to analyze extensive volumes of complex data, identifying patterns and generating valuable insights that contribute to early disease detection, personalized treatment planning, and enhanced patient care. In our analysis, we identified 15 out of the 107 trials within the CV domain that incorporated elements of AI and ML. Table 3 presents a more detailed exploration of these specific trials, highlighting their potential contributions and implications.

Unsurprisingly, most studies concentrated on evaluating the diagnostic capabilities of innovative AI/ML-based platforms. One such study investigated the clinical application of a deep-learning image reconstruction algorithm for the reconstruction of raw CT data of CAD (NCT03980470). The AMPERE study (NCT05362656) is a premarket evaluation of an AI software VX1+ device designed for the detection and automated tagging of spatio-temporal dispersion areas during AF or atrial tachycardia ablation procedures. This evaluation will be compared against manual annotations resulting from operator visual analysis. The BrAID project has developed an integrated platform, employing both ML and omics techniques, to aid physicians in the accurate diagnosis of type 1 Brugada syndrome (NCT04641585). The study includes a prospective component involving 44 patients for Brugada syndrome identification and a subsequent validation study encompassing a cohort of 100 patients. In an innovative application within the realm of emergency care, Copenhagen's emergency medical services have developed a real-time ML model aimed at analyzing "112" (emergency number) calls (NCT04219306). Interestingly, this ML framework has demonstrated significantly faster identification of out-of-hospital cardiac arrest (OHCA) cases compared to medical dispatchers, albeit with a slightly lower positive predictive value, as reported by Blomberg and colleagues.[13]

Additionally, a non-randomized, parallel, open-label study (NCT05903898) has sought to assess whether an AI support tool for radiological image processing, known as StrokeSens, can expedite decision-making and enhance the detection rate in patients with acute ischemic stroke. As StrokeSens carries a CE mark, the primary outcome measure focuses on improving hospital processes. Secondary measures involve evaluating functional assessments relative to the proportion of patients identified with the target diseases compared to standard care. Another study, referenced as DRKS00017160, evaluated on-site ML-based interventions for detecting hemodynamically significant coronary stenosis in comparison to a control group.

We uncovered two studies targeting HF prevention. In the OSICAT study (NCT02068118), a telecardiology program uses automatic algorithms to detect HF-related hospitalization, aiming to prevent all-cause death and unplanned hospitalization through early HF detection. Another study (ISRCTN86212709) uses risk-based algorithmic management by collecting symptoms, physiological data, and system use from home monitoring devices, integrating them with electronic health records for fluid status and risk estimation in HF patients. Two studies (NCT05093803 and NCT04828655) emphasize nutrition, particularly the Mediterranean diet, and physical exercise for preventing CV disease. These studies employ an ML-based app to support self-management, guiding diet and physical activities while monitoring participants' bio

Table 3. Characteristics of CV-related trials involving artificial intelligence/machine learning elements.

ID/Acronym	Condition	Intervention	Objective of intervention	Enrollment	Allocation	Model	Masking	Primary purpose	Funding
NCT03980470	CAD	Deep learning image reconstruction (DLIR) software (TrueFidelity)	Assess potential of DLIR in clinical setting	50	None	Single	Open label	Diagnostic	Academic
NCT05903898	Ischemic Stroke	AI software StrokeSens	Evaluate whether AI support tool accelerates decision making and increases detection rate	1000	NR	Parallel	Open label	Diagnostic	Academic
AMPERE	AF; AT; AA	AI software VX1+	Assess ergonomic function and reliability for dispersed electrograms detection and automatic tagging on 3D map in real time	40	None	Single	Open label	Diagnostic	Industry
BrAID	Brugada Syndrome 1	ECG analysis by ML algorithms	Evaluation of ML algorithms in recognition of Brugada syndrome	144	NR	Parallel	Open label	Diagnostic	Government
NCT04219306	OHCA	ML model that analyzes 911 calls and recognizes suspicion of cardiac arrest	Evaluate whether potential increases in recognitions are due to machine alerts or increased focus of medical dispatcher on recognizing OHCA	5242	R	Parallel	Triple (participant, care provider and outcomes assessor)	Diagnostic	Government
CT FFR	CAD Atherosclerotic CVD	ML Computed Tomography-Based Fractional Flow Reserve (CT-FFRML) with Instantaneous Wave Free Ratio (iFR®)	Evaluate the on-site ML-based intervention for the detection of hemodynamically significant coronary artery stenosis in comparison to the invasive reference standard of instantaneous wave free ratio (iFR®).	50	NR	Single	Open label	Diagnostic	Industry

(continued)

Table 3. Continued.

ID/Acronym	Condition	Intervention	Objective of intervention	Enrollment	Allocation	Model	Masking	Primary purpose	Funding
PROTEUS	CHD	Medical device software (EchoGo) assessing stress echocardiograms and provides classification of risk of CAD	Assessing the ability to make an appropriate referral to coronary angiogram at 6 months following stress echocardiogram.	2500	R	Parallel	Single (participant)	Health Services Research	Industry
CARDIOKIT	Ventricular Tachycardia	CardioKit prototype that monitors cyclical heart-beat motion, cyclical respiratory motion and non-cyclical heart position changes while the patient is lying in supine position	Analyze ultrasound image data quality	24	None	Single	Open label	Other	Academic
NCT04580095	Heart Diseases	AI-based algorithm providing real-time feedback on left ventricular apical shortening	Assess the effect of AI algorithm on image quality in echocardiography	88	R	Parallel	Single (outcome assessor)	Other	Government
OSICAT	HF	Telecardiology program with automatic algorithm for early detection of hospitalization due to HF	Compare rate of all cause deaths and hospitalizations of patients with HF between telecardiology group and control	990	R	Parallel	Open label	Prevention	Industry
NCT05093803	CVD associated with body composition	ML-based app for improvement of health and body composition through guided nutrition and physical exercise programs	Investigate health effects of app on body composition parameters and blood markers	70	NR	Sequential	Single (outcome assessor)	Prevention	Academic
NCT04828655	Hypertension;Diet, Mediterranean; Cardiovascular Diseases; Exercise;Machine Learning; Overweight and Obesity;	ML-based app for improvement of health and body composition through guided nutrition and physical exercise programs	Investigate health effects of app on CV variables and body composition	36	R	Crossover	Single (participant)	Prevention	Academic

(continued)

Table 3. Continued.

ID/Acronym	Condition	Intervention	Objective of intervention	Enrollment	Allocation	Model	Masking	Primary purpose	Funding
	Body Composition; Triglyceride-Storage; Disease								
SUPPORT-HF 2	CVD; HF; Circulatory system	Mobile health home monitoring system for HF patients	Test whether mobile health monitoring system can support HCP in HF patient management	200	R	Parallel	Unknown	Prevention	Government
TICS	Cardiac Valve Disease; Coronary Artery Disease; Surgical Complication	Telehealth monitoring incorporating algorithms for patient feedback for prehabilitation	Improving quality of life prior to surgery and prevent serious deterioration requiring hospitalization	448	R	Parallel	Open label	Supportive care	Government
CLEAR	Consequences of cerebral infarction	Brain-computer interface-based language training	Increase quality of life and autonomy of aphasic patients	14	R	Parallel	Open label	Treatment	Academic

CAD: coronary artery disease; AF: atrial fibrillation; AT: atrial tachycardia; AA: atrial arrhythmia; OHCA: out-of-hospital cardiac arrest; CHD: coronary heart disease; HF: heart failure.

parameters and overall health. In TICS (NCT05621954), telehealth monitoring with AI is explored for cardiac surgery patients. It aims to enhance quality of life and prevent deterioration by measuring vital signs, using customized algorithms, and providing patient feedback for prehabilitation and post-operative monitoring. In PROTEUS, EchoGo, a benchmarked AI software, assesses stress echocardiograms for CAD risk (NCT05028179). Another study (NCT04580095) evaluates an AI algorithm's impact on echocardiography image quality, specifically apical foreshortening in ECG. Additionally, a study (NCT05850741) analyzes a medical device monitoring heartbeat and respiratory motion, focusing on image quality in identifying cardiac cycles, heart displacement, structural distinctions, and image stability. Unlike pharmaceutical trials, only one study (DRKS00031164) explores novel technology for treatment. It introduces a high-intensity language training program for stroke patients with aphasia, providing brain-state-dependent feedback through ML. Results show medium to large and generalized language improvement regardless of initial aphasia severity.[14]

Discussion

In recent years, the field of DHTs and AI has shown great promise in transforming various aspects of healthcare, including CV medicine.[8] In fact, the utilization of DHTs has surged dramatically amid the COVID-19 pandemic.[15,16] Publications reporting the applications of these technologies in the CV space have also been growing, with focus on optimizing patient care and enhancing diagnostic and therapeutic approaches.[8]

Regarding intervention types we noticed that approximately a fifth of all interventions did not fall into any of the conventional categories according to the authors of the studies. However, a closer inspection reveals that out of the 22 studies classified in that manner, 15 could be classified under "device," 15 studies could be argued to employ "behavioral" interventions, while only one study could be classified as "other" (NCT01789554) (Supplemental data). A Karolinska Institute-led study aims to assess the effectiveness of a mobile lifesaver service that localizes and dispatches trained citizens to perform cardiopulmonary resuscitation on OHCA victims (NCT01789554). This intervention does not fall under the definition of a device, nor does it classify as a behavioral approach. Rather, the intervention is focused on taking advantage of available trained bystanders to offer the possibility of rapid assistance, an intervention that we believe does not fall under any classical category. Of note, several studies could be classified as either "behavioral" or "device." For example, studies employing telerehabilitation of HF patients have been classified both as "devices" (NCT01752192 and NCT03388918), "behavioral" (ISRCTN10054455), or "other" (NCT02523560 and NCT05633784). Disambiguation of such cases would be important for maintaining consistency. One way to circumvent that would be by defining "devices" as those interventions by which the main mode of action is delivered by a device (e.g. BP monitor), while "behavioral" interventions would be reserved for interventions that aim to alter patients lifestyles or behaviors even if these are delivered via a device (e.g. educational programs on medication adherence delivered via web-based apps).

Most trials reviewed had relatively small sample sizes, which can be attributed to the novelty and exploratory nature of the studies. Conducting large-scale trials at early stages might be impractical or unfeasible, while the use of smaller studies enables iterative development, allowing applications to evolve continually based on user feedback and real-world implementation. However, to establish the effectiveness of interventions and provide evidence for changes in care, larger trials with robust statistical plans are necessary.

DHT and medical device trials do not have traditional phases. However, we found seven studies following the traditional staging of clinical trials even though none of these studies use pharmaceutical drugs as an intervention. Additionally, the number of participants and outcomes measured do not reflect traditional trial staging. Instead, these could be categorized as pilot/exploratory or pivotal/confirmatory studies. This deviates from the conventional phases of pharmaceutical development, which typically follow a phase 1–4 progression. Instead, the clinical development stages in DHT trials often align more closely with the requirements outlined for medical devices, as delineated in the guideline "Clinical investigation of medical devices for human subjects" (ISO 14155:2020).[17,18] These stages encompass preclinical investigations, feasibility/proof of concept studies, pilot studies, pivotal studies, and post-market surveillance. In contrast to traditional pharmaceutical development, where all phases are usually completed before market authorization, medical device development allows for more flexibility in progression. The pilot stage serves to assess the device's limitations and advantages, including feasibility and first-in-human studies. These assessments are not a prerequisite for advancing to the subsequent stage. Pivotal studies constitute confirmatory investigations aimed at evaluating clinical performance, effectiveness, or safety. Post-market studies aim to establish clinical performance or effectiveness in a broader user and subject population, in accordance with the appropriate guidelines.[17]

While randomized trials continue to be the gold standard in research, our examination revealed a substantial proportion of studies adopting a non-randomized approach. The significance of randomization lies in its capacity to establish comparability among groups, thereby mitigating biases and enhancing statistical robustness. Still, we need to acknowledge circumstances where randomization could be deemed ethically questionable. Additionally, logistical complexities may impede the seamless execution of randomization.

Preliminary exploratory investigations, often undertaken to assess feasibility, may not inherently involve randomization. Resource limitations and longer-time to evidence generation may lead to difficulty in conducting those studies with technologies with such short lifecycles. Similarly, most studies employed parallel assessment, generally accepted as the most standard way of comparing technologies. However, many studies employed single-group assessments, which are particularly employed to assess safety, feasibility, or preliminary efficacy of interventions in early studies. Regarding masking models, more than half (57.9%) of studies did not employ a blinded design. This likely arises from the high number of single-arm studies found, as well as from the difficulty in concealing medical devices and DHTs adequately.[19] These observations align with previous reports on AI trials, which also indicated that most trials had small sample sizes, nearly half of the interventional studies were non-randomized, and only 35% utilized blinded designs. Furthermore, an overwhelming majority of the trials, more than 90%, did not fit into conventional phases of clinical trial classification.[20]

The top researched condition in the CV space was HF. Indeed, applications of AI, in particular the ML subset in HF is expanding, whereby ML algorithms can be applied for the diagnosis, classification and prognosis of the disease,[21] with particular evidence for AI applications in the context of post heart transplantation or mechanical circulatory support, whereby the technology can help for HF outcome prediction.[22] Published evidence has also highlighted AI's growing impact on ischemic heart diseases by aiding diagnosis and treatment. AI-powered tools can interpret ECGs, cardiac imaging, and predict risk, enabling early intervention. These advancements hold potential to revolutionize ischemic heart diseases care, but ongoing research is crucial to fully validate AI's role in enhancing patient outcomes and refining medical strategies. AI can have vast potential in medical imaging, but its application in cerebrovascular diseases is still limited. However, DL methods are promising for imaging to enhance computer aided detection, prediction, treatment of cerebrovascular diseases,[23] and identification of predictive factors for stroke subtyping.[24]

Challenges

A relatively small proportion (less than 10%) of the shortlisted trials have incorporated components of AI/ML, perhaps indicative that the adoption of these technologies in the medical field remains relatively new, with ongoing exploration of formal validation.

With the implementation of the European MDR and IVDR regulations, a considerable amount of medical software will fall under the purview of these regulations. As an example, the Apple Watch was not initially considered a medical device. However, this technology is able to analyze heart rate and detect arrythmias and future features include detecting diabetic levels of patients. As such, it has since been classified as a medical device by the US FDA.[25] In Europe, the ECG app from the Apple Watch has received CE marking for users aged 22 years or older. If the intended purpose of the app goes beyond informative only and provides information that informs or influences medical decisions, it will be considered a medical device as per the definition in the EU MDR.[26] Upon analysis of the primary objectives, we discovered a diverse range of purposes, including treatment, supportive care, prevention, diagnostics, health services research, and screening, in descending order of prevalence. This pattern closely aligns with findings from other reports on digital therapeutics, where treatment emerges as the most common primary endpoint, followed by research, prevention, diagnostics, and other objectives, respectively.[27] DHTs have introduced several enhancements to clinical trials, with the most notable improvements being in enabling real-world data collection outside of traditional clinical contexts and fostering more patient-centered approaches.[28] These advancements are consistent with the trends identified in another report,[8] which emphasizes the increasing integration of digital technologies into healthcare and the growing emphasis on patient-centric care models.

Consequently, clinical investigations will be required to assess the efficacy and safety of a great number of DH solutions. The implementation of trials involving DH solutions presents various challenges, including administrative and logistical hurdles in obtaining ethical approval. Additionally, it demands specialized technical infrastructure, robust data management, extensive study documentation, and adequate training for clinical research staff regarding the applications being used.[29] Ensuring data authenticity, integrity, and confidentiality and selecting the appropriate technology also poses significant concerns for the successful execution of trials involving digital technologies.[30] For medical device software incorporating AI, a major challenge lies in complying with both the MD and IVD regulations, in addition to adhering to the additional AI-specific regulatory frameworks such as the upcoming European AI Act. This will have profound implications for compliance in this area.[31] As AI continues to permeate various aspects of daily life, its potential application throughout the lifecycle of medicines and medical devices, including clinical trials, is becoming evident.[32,33]

While the integration of AI into clinical trials holds great promise, there is a crucial need to address technical issues related to study design and validation of these technologies. To address this concern, the CONSORT-AI guideline was introduced in 2020, aimed at trials evaluating interventions with AI components. It provides a structured approach to designing and reporting such trials, ensuring transparency and consistency in the evaluation process.[34] In addition, other frameworks have been proposed for validating AI in the context of precision medicine. These frameworks outline essential steps, including specifying the intended use of AI, defining the target population, determining the timing for evaluation, data safety concerns, establishing

metrics for AI performance evaluation, and devising procedures to ensure explainability of AI-driven decisions.[35] These frameworks are versatile and applicable to a wide range of therapeutic areas, enhancing the reliability and rigor of AI-related clinical trials.

The need for such guidelines and frameworks is underscored by reports of poor-quality results reporting in AI-related clinical trials.[20] Some studies have identified issues of inadequate adherence to reporting standards, high risk of bias, and a lack of diversity in participant populations. Addressing these shortcomings through comprehensive study designs and validated frameworks will strengthen the credibility and utility of AI-driven clinical trials.[36]

Opportunities

Still, DHTs present significant opportunities. Here, we have only explored DHT as interventions and subjects of investigation. However, these technologies can be used to enable trials to be conducted in a decentralized manner at any time, for reduced time and costs, and improved recruitment and comfort of participants.[37]However, it is crucial to recognize differences in access to the internet and levels of digital literacy may hinder participation in such trials and lead to bias in the selected populations.[28] DHTs can be used to harness real-world, data-driven insights. By integrating diverse and comprehensive datasets, these can offer a holistic understanding of patient experiences, treatment responses, and disease progression in real-world settings. This dynamic approach not only enhances the precision of trial design but also facilitates informed decision-making, enabling researchers to identify optimal patient populations, refine interventions, and navigate unforeseen challenges, ultimately fostering more effective and patient-centered clinical trials.

Conclusions

DH is an emerging and dynamic field, with the potential to reshape CV healthcare by improving diagnostic accuracy, risk prediction, treatment strategies, and patient outcomes. Analyzing clinical trials within this domain reveals a broad spectrum of applications, with medical devices comprising nearly half of all interventions. Heart failure stands out as the most extensively investigated condition within the CV realm. Most studies employed relatively small sample sizes and lack the traditional phases commonly associated with clinical trials. We believe addressing these shortcomings through comprehensive study designs and validated frameworks will strengthen the utility of DHT and AI-driven clinical trials.

Limitations

A limitation of our study relates to the screening of two clinical trials databases, restricting the scope of our findings by potentially overlooking relevant studies available in alternative databases. Furthermore, an additional limitation may arise from the relatively restricted search query for capturing studies, which may have led to the underestimation of studies with interventions identified by different keywords.

Contributorship: FL conceived the study, collected and analyzed data, and wrote the first draft of the manuscript. CM and HD performed critical revision of the article. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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

Funding: The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: FL and CM acknowledges funding support from Portuguese public funding through Investimento RE-C05-i02 – Missão Interface No. 01/C05-i02/2022.

ORCID iDs: Fabio Lampreia https://orcid.org/0009-0006-6374-9459
Hélder Dores https://orcid.org/0000-0002-4736-5221

Supplemental material: Supplemental material for this article is available online.

References

1. *Global strategy on digital health 2020-2025*. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.
2. Healthcare Financial Management Association. *Introduction to digital healthcare technologies*. Bristol: HFMA, 2021.
3. European Federation of Pharmaceutical Industries and Associations. Digital Health, https://www.efpia.eu/about-medicines/development-of-medicines/digital-health/ (accessed 6 October 2023).
4. Food and Drug Administration. What is digital health? https://www.fda.gov/medical-devices/digital-health-center-excellence/what-digital-health (accessed 6 October 2023).
5. Sun X, Yin Y, Yang Q, et al. Artificial intelligence in cardiovascular diseases: diagnostic and therapeutic perspectives. *Eur J Med Res* 2023; 28: 242.
6. Bohr A and Memarzadeh K. The rise of artificial intelligence in healthcare applications. In: *Artificial intelligence in healthcare*. Elsevier, 2020, pp.25–60.
7. World Health Organization. Cardiovascular diseases (CVDs), https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1 (accessed 16 January 2024).
8. Zwack CC, Haghani M, Hollings M, et al. The evolution of digital health technologies in cardiovascular disease research. *npj Digit Med* 2023; 6: 1.
9. Koulaouzidis G, Jadczyk T, Iakovidis DK, et al. Artificial intelligence in cardiology—a narrative review of current status. *J Clin Med* 2022; 11: 3910.

10. European Commission. Getting ready for the new regulations, https://health.ec.europa.eu/medical-devices-new-regulations/getting-ready-new-regulations_en (accessed 6 October 2023).
11. Clinical Trials Arena. Europe accounts for 19.3% share of global clinical trial activity in 2020, https://www.clinicaltrialsarena.com/clinical-trials-analysis/europe-accounts-for-19-3-share-of-global-clinical-trial-activity-in-2020/ (accessed 6 October 2023).
12. An S and Song R. Effects of health coaching on behavioral modification among adults with cardiovascular risk factors: systematic review and meta-analysis. *Patient Educ Couns* 2020; 103: 2029–2038.
13. Blomberg SN, Folke F, Ersbøll AK, et al. Machine learning as a supportive tool to recognize cardiac arrest in emergency calls. *Resuscitation* 2019; 138: 322–329.
14. Musso M, Hübner D, Schwarzkopf S, et al. Aphasia recovery by language training using a brain-computer interface: a proof-of-concept study. *Brain Commun* 2022; 4: fcac008.
15. Meskó B. COVID-19's Impact on digital health adoption: the growing gap between a technological and a cultural transformation. *JMIR Hum Factors* 2022; 9: e38926.
16. Negreiro M. *The rise of digital health technologies during the pandemic*. European Parliament, 2021.
17. Schweizerische Normen-Vereinigung (SNV). Clinical investigation of medical devices for human subjects-Good clinical practice (ISO 14155:2020) Schweizerische Normen-Vereinigung (SNV) Sulzerallee 70 CH-8404 Winterthur, www.snv.ch (2020).
18. Fiedler BA and Ferguson M. Overview of medical device clinical trials. In: *Managing medical devices within a regulatory framework*. Elsevier Inc., 2017, pp.17–32.
19. Huh KY, Oh J, Lee S, et al. Clinical evaluation of digital therapeutics: present and future. *Healthc Inform Res* 2022; 28: 188–197.
20. Wang A, Xiu X, Liu S, et al. Characteristics of artificial intelligence clinical trials in the field of healthcare: a cross-sectional study on clinicalTrials.gov. *Int J Environ Res Public Health* Epub ahead of print 1 October 2022; 19. DOI: 10.3390/ijerph192013691.
21. Averbuch T, Sullivan K, Sauer A, et al. Applications of artificial intelligence and machine learning in heart failure. *Eur Heart J, Digit Health* 2022; 3: 311–322.
22. Al-Ani MA, Bai C, Hashky A, et al. Artificial intelligence guidance of advanced heart failure therapies: a systematic scoping review. *Front Cardiovasc Med* 2023; 10: 1127716.
23. Chen X, Lei Y, Su J, et al. A review of artificial intelligence in cerebrovascular disease imaging: applications and challenges. *Curr Neuropharmacol* 2021; 20: 1359–1382.
24. Miceli G, Basso MG, Rizzo G, et al. Artificial intelligence in acute ischemic stroke subtypes according to toast classification: a comprehensive narrative review. *Biomedicines* Epub ahead of print 1 April 2023; 11. DOI: 10.3390/biomedicines11041138.
25. Food and Drugs Administration. Artificial intelligence and machine learning (AI/ML)-enabled medical devices, https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices (accessed 1 March 2024).
26. The European Parliament. REGULATION (EU) 2017/ 745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL - of 5 April 2017 - on medical devices, amending Directive 2001/ 83/ EC, Regulation (EC) No 178/ 2002 and Regulation (EC) No 1223/ 2009 and repealing Council Directives 90/ 385/ EEC and 93/ 42/ EEC. 2017.
27. Wang C, Lee C and Shin H. Digital therapeutics from bench to bedside. *NPJ Digit Med* 2023; 6: 38.
28. Mittermaier M, Venkatesh KP and Kvedar JC. Digital health technology in clinical trials. *npj Digit Med* Epub ahead of print 1 December 2023; 6. DOI: 10.1038/s41746-023-00841-8.
29. Meyerheim M, Burns-Gebhart A, Mirzaie K, et al. Challenges and pitfalls for implementing digital health solutions in clinical studies in Europe. *Front Digit Health* Epub ahead of print 28 September 2021; 3. DOI: 10.3389/fdgth.2021.730680.
30. Clinical Trials Arena. Ensuring data authenticity, integrity, and confidentiality biggest barrier to using digital technologies in clinical trials: Poll, https://www.clinicaltrialsarena.com/news/ensuring-data-authenticity-integrity-and-confidentiality-barrier-to-digital-technologies-in-clinical-trials/ (accessed 6 October 2023).
31. Life Science Intelligence. Understanding EU MDR approvals approach for AI and ML-Based SaMDs, https://www.lifesciencemarketresearch.com/blog/understanding-eu-mdr-approvals-approach-for-ai-and-ml-based-sa-m-ds (accessed 6 October 2023).
32. Askin S, Burkhalter D, Calado G, et al. Artificial intelligence applied to clinical trials: opportunities and challenges. *Health Technol* 2023; 13: 203–213.
33. Cascini F, Beccia F, Causio FA, et al. Scoping review of the current landscape of AI-based applications in clinical trials. *Front Public Health* 2022; 10: 949377.
34. Liu X, Cruz Rivera S, Moher D, et al. Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension. *Nat Med* 2020; 26: 1364–1374.
35. Tsopra R, Fernandez X, Luchinat C, et al. A framework for validating AI in precision medicine: considerations from the European ITFoC consortium. *BMC Med Inform Decis Mak* Epub ahead of print 1 December 2021; 21. DOI: 10.1186/s12911-021-01634-3.
36. Plana D, Shung DL, Grimshaw AA, et al. Randomized clinical trials of machine learning interventions in health care: a systematic review. *JAMA Netw Open* 2022; 5: E2233946.
37. Inan OT, Tenaerts P, Prindiville SA, et al. Digitizing clinical trials. *npj Digit Med* Epub ahead of print 1 December 2020; 3. DOI: 10.1038/s41746-020-0302-y.