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Key Trends in Digital Health and the Future of Clinical Trials in the US

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A Thesis Submitted in Candidacy for the Degree of Master of Public Health

Yale School of Public Health

Chronic Disease Epidemiology

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Abstract

With the increasing burden of chronic diseases on the global population, many stakeholders see digital health technologies and devices as potential solutions to improve patient self-management of their disease and offer novel treatment methods. Digital health solutions including mobile apps, web-based programs, texting, and connected devices have been applied to a wide variety of diseases. In recent years, interest in digital health technologies has exploded with almost 200 digital health related articles published in PubMed in 2019 alone. In particular, digital health holds great potential in improving and enhancing the traditional clinical trial by increasing patient recruitment and retention and introducing novel assessment and collection methods that shift clinical trials from the physical site to the patients' home. Digital health is poised to fundamentally shift how clinical trials are conducted. However, serious challenges from potential regulatory restrictions and data privacy issues will need to be addressed before patients, physicians, and other stakeholders can fully realize the benefits of digital health.

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Acronyms

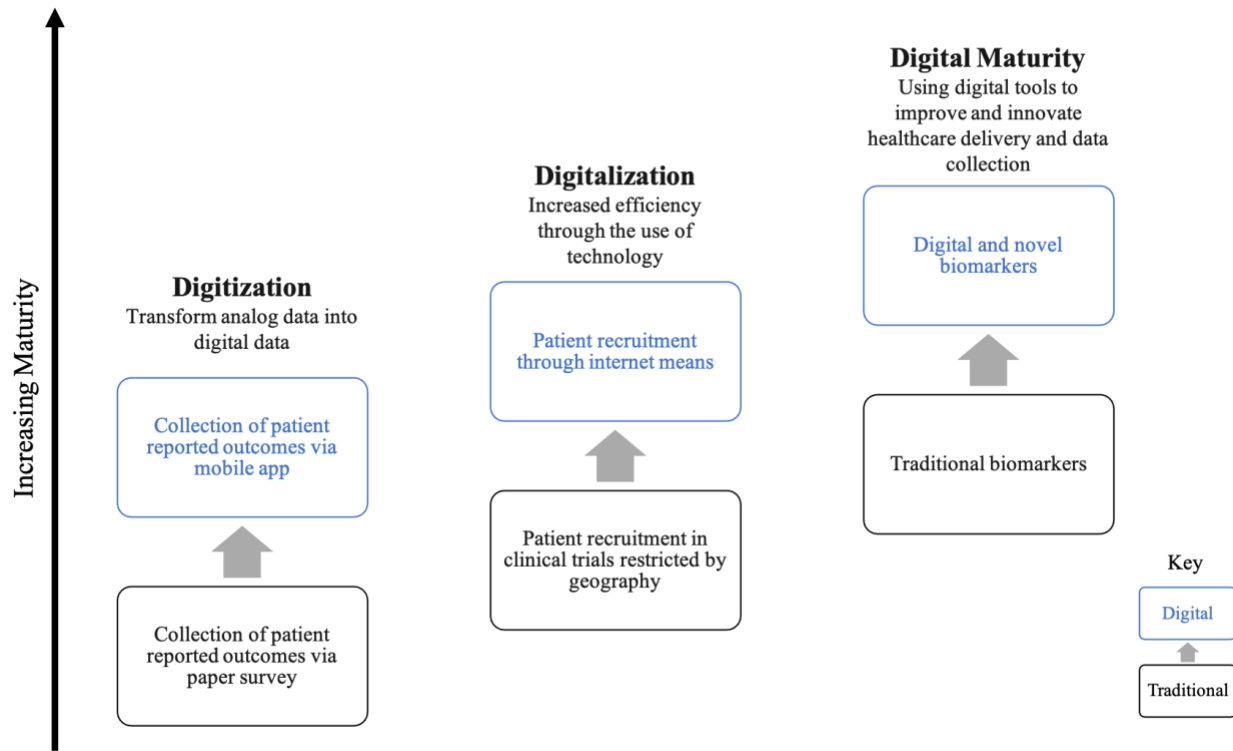
Acronym	Definition
ADHD	Attention-Deficit/Hyperactivity Disorder
AI/ML	Artificial Intelligence/Machine Learning
CBT	Cognitive Based Therapy
CDC	Centers of Disease Control
CIED	Cardiac Implantable Electronic Devices
CIED	Cardiac Implantable Electronic Device
CMS	Centers for Medicare & Medicaid Services
DHCoE	Digital Health Center of Excellence
DTx	Digital Therapeutics
EHR	Electronic Health Record
FDA	Food and Drug Administration
NLP	Natural Learning Processing
PrEP	Pre-Exposure Prophylaxis
PRO	Patient Reported Outcomes
SaMD	Software as Medical Device
SMS	Short Message Service

Introduction

Addressing chronic disease is one of the greatest public health challenges of the modern era. According to the Centers for Disease Control, 6 in 10 US adults suffer from a chronic disease and 4 in 10 US adults have two or more chronic conditions (Centers for Disease Control and Prevention [CDC], 2021). There is an increasing prevalence of chronic conditions and comorbidities with more than half of older adults having three or more chronic conditions, such as diabetes, cardiovascular disease, cancer, arthritis, mental illness, or high blood pressure (American Geriatrics Society, 2012). By 2030, an estimated 170 million Americans will have a chronic disease, a staggering increase from 118 million individuals in 1995 (Newman, 2020). There is greater healthcare cost and service utilization for patients with chronic disease, where those with more conditions have higher associated costs (CDC, 2021). Americans with five or more chronic conditions require 14 times more spending than those with no conditions and represent 41% of total healthcare costs despite only representing 12% of the population (Buttorff et al., 2017). Chronic diseases can have a serious impact on quality of life and lead to future disability, thus posing an even greater burden on health services. Many chronic diseases are caused by identifiable risk factors and behaviors. Avoiding these key factors and maintaining a healthy lifestyle can greatly reduce the likelihood of getting a chronic disease. Health literacy and education can play a critical role in informing patients of regularly exercising, eating healthy, getting properly screened, and avoiding risky behaviors (Poureslami et al., 2017). For those already suffering from a chronic condition, taking their medication is critical to maintaining their health and preventing future disability. However, medication adherence is a serious problem and it is estimated that patient may be nonadherent to their medications 50% of the time (Brown et al., 2016).

Digital health has been seen as a device or tool to facilitate aspects of healthcare from screening, diagnostics, preventative care, and treatment. These devices may serve to support existing health interventions or act independently to improve health outcomes. Digital health can be utilized in many forms but by enabling and encouraging patients to play active roles in managing their health, there has been a focus on their use in chronic diseases and long-term self-management. Basic use of digital health may simplify healthcare through digitization, changing the method of data collection from paper to digital means. One prominent example is the almost ubiquitous use of electronic health records (EHR) over paper forms. However, as digital health evolves, there is increasing focus on digitalization, where current processes are improved and altered through the use of digital health such as online patient recruitment or medication tracking. Recruitment via online modalities has been found to be cost-effective, faster, and achieves higher recruitment rates compared to traditional methods (Brøgger-Mikkelsen et al., 2020). Quisel et al (2019) found that those who actively used their digital health activity trackers were more likely to be adherent to their cardiovascular medication. Digitalization may encourage fundamental behavior change in patients through improved efficiency in current process that lower barriers to better health behaviors. Digital maturity is the ultimate form where digital health is utilized to innovate and fundamentally alter the healthcare paradigm. This is an area that is yet to be explored but a revolution in healthcare will occur when patients, physicians, and other healthcare stakeholders can integrate mature digital health devices and tools into regular care (Figure 1).

Figure 1. Digital Health Maturity with Examples



Regardless, the digital health field is manifesting in many forms from mobile devices, software as a medical device (SaMD), wearable devices, telemedicine, digital therapeutics, and connected drug combination products. The potential of digital health in reducing ever-growing healthcare costs, improving outcomes, and providing new treatment modalities cannot be understated. Sophisticated digital health technologies can monitor patient outcomes, address gaps in patient care, and even support medication optimization. Digital health has been explored as a possible solution to issues surrounding adherence, patient administration techniques, disease self-management, and data outcomes at scale (Bittner, et al., 2019). These technologies are rapidly expanding to provide new and innovative ways to improve health outcomes and many healthcare stakeholders are exploring how digital health can be used.

Clinical trials have become increasingly costly following Eroom's Law, an observation that drug discovery is becoming slower and more expensive despite technological advancements (Scannell et al., 2012). Developing these technological advancements is extremely costly, and study sponsors are under intense scrutiny from competitors, regulatory agencies, and consumers to develop effective products. Fierce competition to develop more complex drug products and meet FDA requirements has resulted in a convoluted clinical trial process. DiMasi (2016) found that the number of study endpoints required by the FDA increased by 86% from 2001-2005 to 2011-2015 and almost 60% of protocols required a major amendment, which came at a median cost of \$141,000. As a result, biopharmaceutical companies are looking at how digital health cannot only reduce costs, patient burden, and reliance on in-person clinic visits but also improve outcome measurements and validation methods. Traditional clinical trials are heavily restrained by cost, duration, and patient engagement. Throughout the course of a traditional clinical trial there are many lost opportunities to monitor a variety of endpoints for disease progression, pharmacokinetics, pharmacodynamics, and safety beyond periodic assessments. End points that are monitored may be heavily dependent on patient engagement and willingness and be subjected to reliability and validity concerns. Furthermore, the trial endpoints may fulfil FDA requirements for drug approval but could be a measurement that is not necessarily meaningful to patients or healthcare providers. The biopharmaceutical industry has recognized the potential of digital health and is driving innovation with guidance from the FDA's newly established Digital Health Center of Excellence (DHCoE) and other regulatory agencies (Food & Drug Administration [FDA], 2020).

The application and value of digital health to clinical trials is currently being explored. These so called decentralized, siteless, remote, or virtual clinical trials integrate digital health in the

delivery of care to move the trial outside of the clinic and enable remote and real-time collection of traditional and novel data. Ideally, digitalization would improve recruitment and retention, data collection, and analytics (Inan et al., 2020). Clinical trials have consistently had low patient adherence and persistence where Murthy et al. (2004) found that only 8% of cancer patients enroll in clinical trials. Recruitment and retainment using digital methods increases access to appropriate and diverse patient populations. Clinical trial language is often confusing to patients and they may not know what participating in a clinical trial may require of them. Having clear guidelines and directions delivered digitally could ensure patients understand the requirements needed from them to participate in the clinical trial. Additionally, patients recruited through relevant online health communities may be more engaged and willing to complete the clinical trial, resulting in better data to determine drug efficacy. With digital recruitment strategies, communication methods can be more tailored towards the targeted population to overcome communication barriers or issues of mistrust and fear in ethnic groups. Decentralized trials will enable participants to take part in a clinical trial regardless of their location, considerably reducing patient burden for travel. Even in so called hybrid trials, where a portion of the clinical trial is still conducted at a study site, there is still improved accessibility. Patients may be required to meet the investigator in the beginning of the trial but could transition completely to virtual meetings as the trial proceeds. Furthermore, telemedicine can improve communication between patients and investigators by providing a method for patients to ask questions. For investigators of clinical trials, a virtual trial allows them to oversee more patients in a larger area compared to traditional clinical trials that limited their oversight to their site. Digital health tools can collect more data thorough patient-reported outcomes (PRO) and biomarkers through technologies such as wearable and mobile sensors. Digital biomarkers, physiological or

behavioral measurements collected with a digital device, could revolutionize the types of endpoints investigators use to test efficacy (Coravos et al., 2019). The data from digital biomarkers is continuously captured and could provide investigators a fuller picture of the patient's health and their response to treatment. With enormous amounts of data, treatments can be better tailored or even personalized as more data is fed into algorithms (Coravos et al., 2019). Critically, decentralized trials are less expensive because of the advantages of technology. A single investigator may oversee a larger number of patients that previously would have required multiple sites and staff to manage. Faster recruitment and lessened burden on patients could shorten trial duration and speed results. Furthermore, by reducing the need for a physical site, sites may be able to oversee more clinical trials simultaneously (Douglas, 2019).

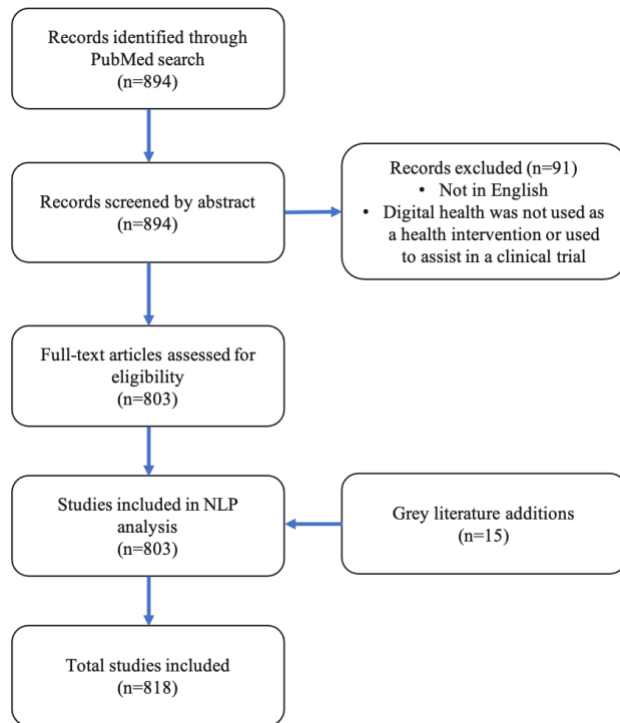
Methodology

Digital health is defined as the use of digital devices, tools, technologies, and services by healthcare stakeholders (patients, providers, organizations) to empower individuals and populations to manage their health and wellness (Snowdon, 2020). Based on this definition and in the context of clinical trials, a PubMed search was conducted using the key words: clinical trial, digital health, ehealth, mobile health, mhealth, siteless, smartwatch, decentralized, remote monitoring (Figure 2a). The PubMed search included studies from inception of the database to January 11, 2021 and had no restrictions on the country of origin. Studies were excluded for not being in English or irrelevancy because digital health was not used to support or act as a health intervention. The search yielded 894 results and 91 were excluded, resulting in a total of 803 relevant records which were analyzed using natural language processing (NLP) for similarities and trends. An additional 15 relevant grey literature, white papers or industry articles, were also included in the review.

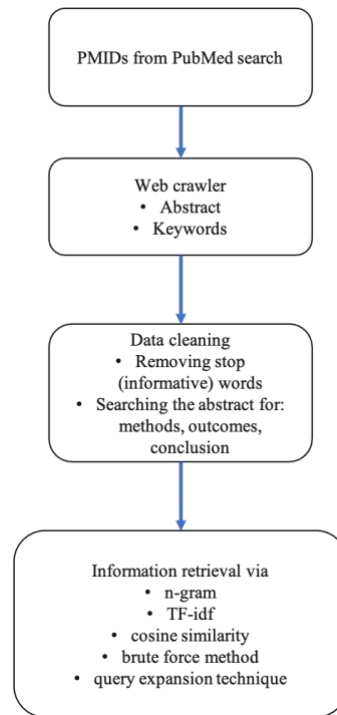
The NLP was performed based on the PMIDs from PubMed selected from the literature review (Figure 2b). A web crawler was used to extract the articles' abstract and keywords followed by data cleaning, removing stop (informative words) and searching the abstracts for the methods, outcome, and conclusion sections. Information retrieval was conducted using NLP processes including n-gram, TF-idf, brute force, cosine similarity, and query expansion technique to extract the keywords and frequency.

Figure 2. Methodology

a. Literature Review Methodology



b. NLP Methodology



Literature Review

Digital Health and Clinical Trials

Digital health in clinical trials has manifested in the literature in two distinct ways, exploring the potential of digital health or capitalizing on digital health to advance clinical trial research. The

majority looked to validate the digital health technology in improving health outcomes or better understanding users' preferences and attitude. Clinical trials were traditionally designed specifically to test the effectiveness of the digital health tool through randomization in intervention and control groups. However, given the emerging digital health field, many of these clinical trials are protocols with studies currently in progress or feasibility studies that merely explore the potential of digital devices. It is unsurprising that many articles are exploratory rather than experimental as it is clear the digital health field is still being developed and the literature centered around investigating the potential benefits of digital health. Due to the slow nature of the pharmaceutical industry to adopt new technologies or methods to their processes, it is likely that industry members will be hesitant to use digital health until the technologies are more mature and have been properly validated to demonstrate value to multiple stakeholders.

Additionally, while some digital health devices may demonstrate efficacy, the extent of these benefits may be limited and are insufficient to drive fundamental change in the industry. While there has been a shift in thought towards how clinical trials could incorporate digital health to collect traditional and novel data, there is still minimal movement by most pharmaceutical companies. However, digital health will likely play a more prominent role especially with the COVID-19 pandemic that has estimated to have stopped nearly 6,000 trials in the first half of 2021, more than twice as many compared to previous years (Gaudino, 2020). Many trials currently in progress have been forced to adopt some virtual components to become entirely virtual or at least partially (Anthes, 2021). Johnson and Johnson's phase 3 COVID-19 vaccine is using a decentralized or virtual trial platform and even post-pandemic this virtual format is likely to remain (Adams, 2021).

The literature review revealed 9 major different types of digital health tools and devices that are being explored and can be split into two major categories: mature devices adopted for use in healthcare and technologies specifically designed to be used in a digital health platform.

Types of Digital Health in Clinical Trials

Table 1. Types of Digital Health Present in Clinical Trials

Type of Digital Health	Definition	Example
Mobile Applications	Software installed on a smartphone, tablet, or similar handheld device that performs a specific health function	Mobile app used to track medication adherence
Smartphone	Using inherent capabilities of the smartphone such as camera or accelerometers	Smartphone urinalysis testing
Web-based	An intervention that is delivered through a computer or website	Interactive or educational modules
Remote Monitoring	Devices that allow continuous and real-time monitoring of patient health	Implantable Cardiac Devices
Texting	Using any mobile device to send messages	Daily text reminders
Telehealth	The delivery of healthcare from one site to another using electronic communication methods such as video conferencing	Video health consultations
Wearables	Small electronic devices worn on the body that contain sensors to track different measurements	Smart watch
Connected Devices	Digital tools that do not fall into the above categories	Smart inhaler
Other	Other digital tools of interest such as the artificial pancreas, smart pills, smart pill bottles, and smart scales	Smart bioingestible pill

Mobile Apps

The most commonly used digital health tool found in the literature search was mobile applications (mobile apps). Mobile apps are specific software that is installed by the user onto their smartphone, tablet, or similar handheld device. This patient facing tool allows users to provide relevant data through the mobile app which collects the data to be shared with the researcher. In recent years, this category has exploded in popularity as barriers to the development of mobile apps have significantly decreased. Furthermore, smartphone ownership

has continued to rise where an estimated 1/3 of the world's population has a smartphone (Reisinger, 2014). The number of health-related apps available to any user to download exceeded 325,000 in 2017 with more than 80,000 publishers (Globe Newswire, 2020). The type of mobile app can vary widely depending on its intended use and therapeutic area. Apps can be used to simply remind patients to take their medication or record daily PROs such as their mood or symptoms. Complex apps would not only solicit PROs but use passive monitoring data inherent to the device. Some may facilitate tests to measure specific digital biomarkers to track disease progression. Other apps may be an intervention itself designed to create behavioral change. One popular form is gamification, where game-like elements are integrated into the mobile health app to encourage patients to perform positive behaviors (Zolfaghari et al, 2021). Most apps focus on simple interventions that require minimal software skills and consequently offer limited value. Sophisticated features such as machine learning are rare. Despite the widespread popularity of mobile health apps, there is limited regulation or validation that using such mobile apps can change behavior or improve health outcomes. Critically, very few of these mobile apps have demonstrated clinical efficacy. Thus, it is unsurprising that 41.85% (113/270) of the studies in the literature review that had a mobile app component were protocols or feasibility studies. The prevalence of exploratory studies indicates significant questions remain about the utility of mobile health apps. The results of studies utilizing mobile apps vary widely from demonstrating a successful intervention to having no effect. StressLess, a mental health app for caregivers, reduced stress and depressive symptoms among users in the intervention group over 5-weeks. However, on average participants only completed 2.5 of 5 treatment modules and 25% of participants were lost to follow-up (Fuller-Tyszkiewicz et al, 2020). In contrast, CONNECT, an EHR-integrated app focused on improving medication adherence, demonstrated no significant

difference between the intervention and control groups for adherence but marginal improvements in other components such as e-health literacy (Redfern et al, 2020). Common limitations with mobile app focused studies involve possible sampling bias and generalizability to the wider target population. Despite online recruitment methods through Facebook and other social media sites, some studies struggled to meet sample size targets resulting in underpowered studies. Others required the participant to have an iOS or Android device to download and use the mobile app. Studies whose apps are restricted to iOS devices may be even more biased given the significantly lower markets share of iOS devices (27.47%) compared to Android devices (71.93%) (Statcounter, n.d.). Lastly, many mobile apps often rely on self-reported outcomes of wellbeing or participation and are at risk for the Hawthorne effect where participants behave differently because they know they are being observed.

Smartphones

A related digital health utilization of smartphones focuses on the inherent capabilities of the smartphone itself. Rather than a conduit for other software or mobile apps, the smartphone itself is the digital technology. Most commonly used in a diagnostic manner, patients utilize aspects inherent to the device, such as the camera by taking a photo and sending it to their healthcare professional (Uthoff, 2020; Leddy, 2019). The smartphone can allow point of care testing, where healthcare or treatment and disease diagnosis can be delivered to the patient at the time of care (Kost, 2002). This could greatly speed diagnosis and reduce the need for in-person visitations, freeing up healthcare services. Some studies have shown success such as Dip.io, a smartphone urinalysis test that screens for proteinuria to identify those with hypertension for possible kidney disease (Leddy, 2019). Individuals were able to screen themselves from their home and use of the kit can improve proteinuria screening rates (Leddy, 2019). Limitations of

smartphone-based studies follow closely with mobile app studies because of the reliance on smartphones. Additionally, these studies may require additional support from clinicians and laboratories to conduct the test or screening. Collection of the biological sample may be done at the patients' convenience but testing and analysis must still be conducted by a healthcare professional. The independence and self-management aspect associated with mobile apps does not extend for these smartphone-based screening or diagnostic tests.

Web-Based

Web-based or internet-delivered interventions is an expansive category where digital health is primarily delivered through a computer but the intervention is often supplemented with additional digital tools. Patients can access the intervention through a website that exists as a central hub for their health data (Moore et al., 2020). Patients may need to complete modules consisting of videos with follow-up activities or assignments. One prominent example of this category is internet-delivered cognitive behavioral therapy (CBT). Cognitive behavioral therapy has been extensively studied in a number of diseases including insomnia, anxiety disorders, and major depression. Internet-delivered CBT has been explored and most studies find that it is comparable to in-person CBT (Bergström et al., 2010). Furthermore, internet-delivered CBT offers additional benefits such as eliminating travel barriers. While care can be delivered in real-time, it is not necessary, allowing patients to move through the therapy at their pace and give clinicians ample time to respond to questions or consult colleagues. Sleepio, a CBT study for insomnia to treat depression, demonstrated patients in the intervention had significantly lower depression severity compared to the control group (Cheng et al., 2019). While web-based interventions caught on early with the advent of computers, it is clear that stakeholders are moving away from these

computer-based tools. Most digital health tools today are either directly optimized for smartphone use or offer a mobile version.

Remote Monitoring

Remote monitoring is the monitoring of activities that were previously conducted on site in a clinical trial. Furthermore, with continuous and real-time monitoring, more data can be collected to be analyzed and abnormal events can be detected. This allows investigators to frequently evaluate patient safety and monitor other critical indicators such as medication adherence or treatment compliance (Patel, 2017). Remote monitoring is one of the earliest forms of digital health that showed significant interest because of inherent monitoring capabilities in cardiac implantable electronic devices (CIEDs). Numerous studies have shown that remote monitoring of patients with CIEDs is associated with earlier detection of actionable events, lower hospitalization, and lower mortality (Pluta et al, 2020). In the HomeCARE-II study, patients were remotely monitored through their implantable devices to validate another measurement for fluid accumulation (Maier et al., 2019). There has been particular interest to apply remote monitoring beyond cardiovascular monitoring because of the high cost of traditional monitoring which typically accounts for 25% of a clinical trial's total budget (Scannell et al., 2012). The EDGE system used commercial pulse oximeters to remotely monitor patients for one year to develop an algorithm that predicts COPD exacerbation events (Shah et al., 2017). By combining the vital signs obtained from the pulse oximeter, the researchers were able to predict events with 60%-80% sensitivity and 68%-36% specificity (Shah et al., 2017). The potential of remote monitoring depends on the detection of validated measurements that can be predictive and informative of future events. As technology advances, more forms of remote monitoring will emerge that can be greatly expanded beyond cardiovascular disease. Challenges with remote

monitoring center around interoperability and the need to integrate remote monitoring data with the patient's electronic health record (EHR) (Yamada et al., 2020). Furthermore, while patient burden is lessened by minimizing travel to the site, there is greater responsibility placed on investigators to parse through the data. Depending on complexity of the remote monitoring system, clinician or statistician workload could substantially increase depending on amount of data that needs to be processed.

Short Message Service (SMS)

Prior to the development of smartphones, short message service (SMS) or texting was a popular digital health tool to deliver helpful information of patients in self-managing their disease.

Texting is a low-cost digital health tool because it only requires a mobile device, not a smartphone. As a result, many studies using texting are localized in developing countries where mobile phone use is more common or for older populations who may struggle to use smartphones. The LEAN program utilized texting and lay health supporters to improve schizophrenia care in rural China and demonstrated improvements in medication adherence, improving symptoms, and reducing rehospitalizations (Cai et al., 2020). Even for younger populations, texting is still a popular form of digital health even among those with smartphones and mobile apps because of its ease of use and low burden on the user. Guy2Guy, an HIV prevention program for minority youths, specifically utilized texting because of the prevalence of cell phones even in underserved and low-income populations (Ybarra et al., 2018). Furthermore, texting-based interventions are very cost-effective compared to in-person and web-based interventions. In Guy2Guy, sending and receiving text messages cost less than 2 cents per message (Ybarra et al., 2018). While pre-exposure prophylaxis (PrEP), medication that prevents HIV infection, has been proven to be highly effective, reducing the risk of HIV infection by

99%, its prohibitive cost at \$2,000 a month is a major barrier for the populations at risk for HIV (Grant et al., 2010). Digital health interventions such as texting can be a suitable alternative. Similarly, many low-income families may not have computers but most have a cell phone with texting capabilities and thus interventions with texting may be an effective path to targeting a specific demographic.

Telehealth

Telehealth is the delivery of healthcare from one site to another between the patient and provider using electronic communication methods such as video conferencing or telephone calls (Centers for Medicare & Medicaid, 2020). Video visits have been viewed as a low cost and convenient method to deliver care to patients, especially those in rural areas where transportation is a major barrier to accessing care. Similarly, telephone calls are potentially more convenient to patients who have difficulties accessing the internet or using a computer. The capability to provide synchronous or asynchronous care without regard to distance, while still conforming to regulatory policies, has been seriously studied to some success. The telehealth intervention in the Healthline services was found to be associated with only minor clinical benefits for most individuals and no overall improvement in risk (Salisbury et al., 2016). Another trial from the Minneapolis Veterans Affairs Health Care System did not find any statistically significant difference between the standard of care and telehealth (Ishani et al., 2016). The use of telehealth in clinical trials appears to be limited but there is significant interest in validating the use of telehealth across a number of therapeutic areas.

Wearables

Wearables are small electronic devices worn on the body as accessories that contain one more sensor. Common devices include watches, belts, glasses, or adhesive patches. The sensors in

wearables can track a number of different measurements from movement and position, electrophysiological or chemo-physiological function, or other physiological properties.

Wearables in the form of watches, or smartwatches, have recently become exceedingly popular with users as they are able to track their health data in real-time. Features that attract patients include the ECG on the Apple Watch that was approved by the FDA to detect atrial fibrillation (Wetsman, 2020). Although studies only show moderate diagnostic accuracy, this technological advancement is a shift towards increase patient self-management of their health via personalized devices (Rajakariar et al., 2020).

Connected Devices

There are a number of additional digital health tools that are beginning to see usage. Smart scales are electronic weight scales that have a mobile app companion that allows users to track their weight and may be particularly useful for those with diabetes. Artificial pancreas for type 1 diabetes are sophisticated systems that combine an insulin pump and continuous glucose monitor and use an automatic algorithm to administer real-time basal insulin delivery to patients (Forlenza et al., 2019). Such systems have been proven to significantly improve glycemic control and represent a perfect unity of digital health technologies to improve health outcomes. An ingestible smart pill has also been explored to track adherence but it has struggled to gain traction due to a number of core issues (Chai et al., 2017). Proteus Digital Health originally tested their smart pill in type 2 diabetes, finding that the pill and associated digital health offerings could assist in lowering blood pressure, blood sugar levels, and other associated outcomes but they track adherence levels (Frias et al., 2017). However, Proteus decided to target neurological disorders using the generic schizophrenia and bipolar disorder drug, Abilify. The cost of the generic drug, at \$500-\$800, combined with the device resulted in a drug-combination

device of more than \$1,600 (Landi, 2020b). This prohibitive cost in a small, disease-specific population combined with mixed results of the technology resulted in Proteus filing for bankruptcy (Landi, 2020a). Other drug-device combinations have shown some clinical efficacy such as the BETACONNECT system which combines an autoinjector that tracks medication adherence with additional digital health tools to address the needs of patients with multiple sclerosis but overall adoption is still limited (Limmroth et al., 2018). A successful drug-device product is Propeller Health's connected asthma inhalers. In multiple studies, Propeller has demonstrated improved adherence, fewer symptoms, and less asthma-related emergency room visits (Merchant et al., 2016). Furthermore, this clinical efficacy has translated into commercial success in 2019 when Propeller was acquired for \$225 million (Licholai, 2019). Additionally, Propeller revenue model is based on partnerships with pharmaceutical companies and health systems with no cost to the patient. (Moukheiber, 2018).

Other

Although most digital health tools have patient-centric designs, focused on patient satisfaction and needs, not all tools are made for patients. A number of digital platforms and clinical decision support services were designed specifically for physicians and nurses to use. These digital tools aid healthcare providers by streamlining the care process.

These digital health technologies should not be viewed as separate entities where patients are only using one device or tool. Skill to Enhance Positivity (STEP), combined weekly phone calls with daily text messages and was found to reduce suicide events in adolescents over a 6-month period (Yen et al., 2020). In many cases, mobile apps were paired with a wearable where data from the wearable could be directly viewed by the user through the mobile app. STEP UP combined a gamification app and wearable device to encourage participants to improve their

physical activity (Patel et al., 2019). By tracking their daily steps through the wearable and participating in the game through their app, participants had significantly increased physical activity compared with the control group (Patel et al., 2019).

Prominent Therapeutic Areas with Digital Health

Digital health tools are used across a variety of therapeutic areas from oral health and HIV to maternal health and cardiovascular disease. Given the flexibility of digital devices, it appears that any disease or therapeutic can utilize these devices to improve health outcomes. However, there are certain therapeutic areas that dominate because of the high prevalence and incidence of the disease. Specifically, diabetes, cardiovascular disease, and mental health appear to be particularly attractive targets for digital health.

Diabetes and Wellness

Diabetes and general health wellness through dieting and exercise is a major target for many digital health devices or interventions. Diabetes is a complex disease with many stages that require different methods of treatment. Earlier stages of diabetes focus on addressing lifestyle changes and better health education to improve outcomes. Diabetes self-management education has been shown to improve glycemic control and is a considerably easy method to address diabetes. With current technological advancements, delivery of training tools to individuals to assist them in self-managing their disease is an effective way to address diabetes. Unregulated digital tools are abundant from untested or validated mobile health apps that claim to improve diet and exercise. Furthermore, existing studies on health apps show limited improvements across a number of outcomes including glycemic control, weight loss, or medication adherence (Shah, Garg, 2015). However, there is evidence that the use of mobile apps in a weight loss program results in greater weight loss compared to a program without using an app (Turner-

McGrievy et al., 2013). Approved digital tools such as insulin pumps, artificial pancreases, and continuous glucose monitors have demonstrated substantial evidence in improving health outcomes. These devices have undergone numerous cycles of development. In addressing the lack of improvements from using mobile health apps, some developers are investigating gamification to improve physical activity and diet (Boulos et al., 2015).

Cardiovascular

Cardiovascular disease and other related health issues such as heart failure have become a serious issue in older adults who are at particularly high risk. These individuals may have multiple comorbidities and infirmities that limit their ability to maintain their health and have difficulties seeking healthcare. Digital health is seen as an opportunity to address gaps in care. Besides the common benefits of digital health across any therapeutic area, patients with cardiovascular disease may benefit from telemedicine and remote patient monitoring.

Telemedicine can eliminate barriers of transportation which are particularly troublesome for older adults. Furthermore, remote patient monitoring can capture and monitor vital signs and biometrics (Krishnaswami et al., 2020). Although previous studies have shown older adults underutilize digital health technologies, this is rapidly changing with the COVID-19 pandemic. Given the high prevalence of cardiovascular disease in older patients, digital health could provide better real-time data for healthcare providers and result in quicker decision making and detection of adverse events.

Furthermore, with the popularization of commercial ECGs via the Apple Watch, preventative care is also possible. Although most digital health has centered around remote monitoring through CIEDs, there is a shift towards using these devices to detect irregularities in an individual's health.

Mental Health Disorders

Mental health disorders is a unique category that has been receptive to digital health interventions. The prevalence and incidence of mental health problems in children and young adults has been significantly increasing (Collishaw, 2015). This has been followed with an increased demand for mental health services on an already stressed healthcare system. Digital health devices and interventions are seen as scalable tools that improve access and meet needs (Hollis et al., 2017). Internet-delivered CBT is a popular intervention for mental health disorder but there is an increasing interest in adapting mobile health apps that focus on wellness.

Discussion

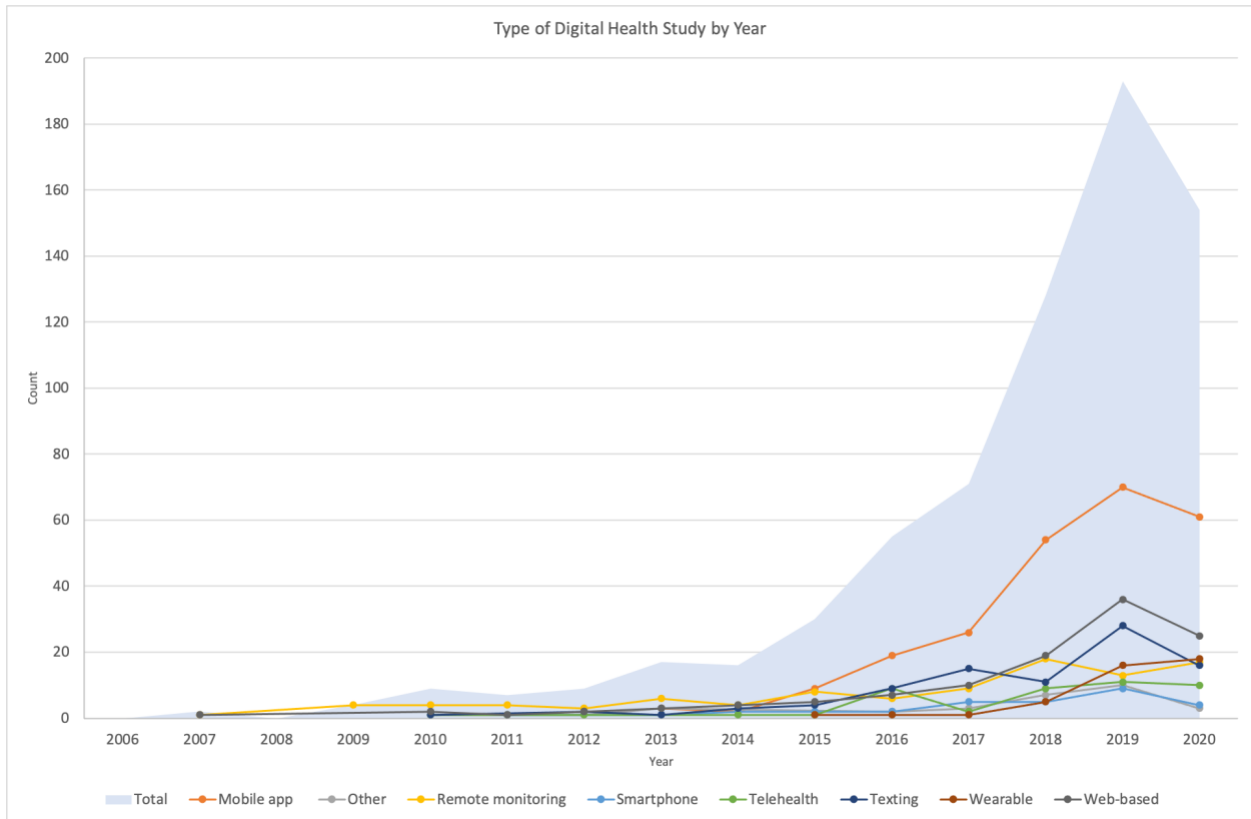
The Increasing Presence of Digital Health

Digital health is undoubtedly of great interest to all stakeholders in healthcare from patients, physicians, healthcare organizations, to pharmaceutical companies. This interest is reflected in the large number of peer reviewed articles published in PubMed. Figure 3a shows the number of digital health studies published each year from 2005 to 2020 and the main digital health technology in the article. There has been exponential growth in the number of published digital health articles in the last few years. Although there has been consistent interest in digital health technologies, this interest began picking up in 2010 due to a variety of factors that created opportunities for exploration in digital health. The Obama administration wanted to revolutionize healthcare and pushed the adoption of electronic health records to improve the quality of care. Furthermore, cell phones had become increasingly common place and advanced, with smartphones emerging onto the market. This paradigm shift in the US from paper to electronic methods created a prime environment to combine health and technology. The ubiquity of smartphones and ease in creating mobile applications is reflected in the Mobile app category

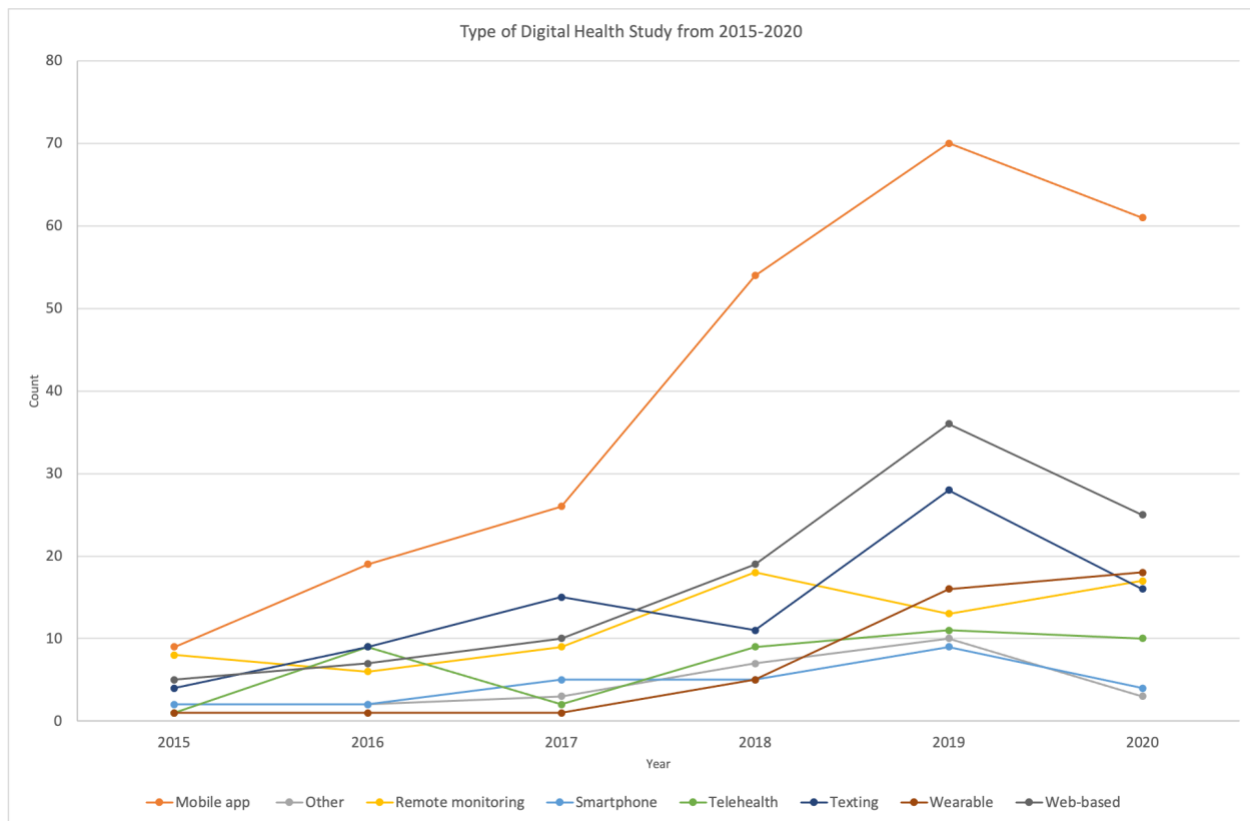
having the highest number of articles. All other categories fall short in matching the apparent interest stakeholders have in creating healthcare solutions through mobile apps. However, there are a number of notable categories that demonstrate shifting interests. Remote monitoring has shown a consistent presence due to the use of CIEDs, which inherently have an automatic monitoring component, but there has been new interest in remote monitoring beyond monitoring for heart failure alone.

Figure 3. Number of Studies by Digital Health Device

a. Total Number of Digital Health Studies from 2006-2020 by Digital Health Device



b. Number of Digital Health Studies from 2015-2020 by Digital Health Device



The sharp decrease in total number of articles published in 2020 can be attributed to the COVID-19 pandemic. Future and current clinical trials were impacted and in some cases were placed on hold. These delays in research impacted the ability of investigators to conduct their studies and subsequently publish their data. Furthermore, some investigators who already completed their trials and were pursuing publication may have experienced delays in the review process.

Similarly, journal editors may have struggled to review submissions in a timely matter and find appropriate individuals to peer review incoming articles. As a whole, the entire process from collecting data to publishing an article was impacted by COVID and is clearly reflected in the 20.72% drop in articles in 2020. Figure 3b gives an in-depth view of trends from 2015-2020.

Besides mobile apps, the number of articles on web-based solutions and texting increased.

Increased interest and demonstrated effectiveness of CBT could be attributed to the growth in

the web-based category since many of those interventions are delivered via the web. Similarly, the increasing prevalence of mobile phones combined with the low cost associated with texting interventions likely fueled interest in texting. In contrast, smartphones may have a more prohibitive cost making it less attractive digital health intervention.

The use of the term ‘digital health’ has not been ubiquitous in addressing the use of technology in healthcare. While ‘digital health’ is now used as the overarching term many sub-terms are often used more commonly in the literature. Figure 4 lists the top terms used in the abstracts of articles in the literature review to refer to the use of technology in the clinical study. ‘mhealth’ is the most commonly used term by far, demonstrating the popularity of mobile technology in healthcare. While ‘ehealth’ is used as a broad term to encompass the use of electronic means in the delivery of healthcare. These two terms represent the vast majority of digital health clinical trials, using mobile devices or electronic devices. Telemedicine and telehealth are another aspect of digital health that often is ignored when considering digital health as a whole. Other variations appear in the literature but representative a small proportion.

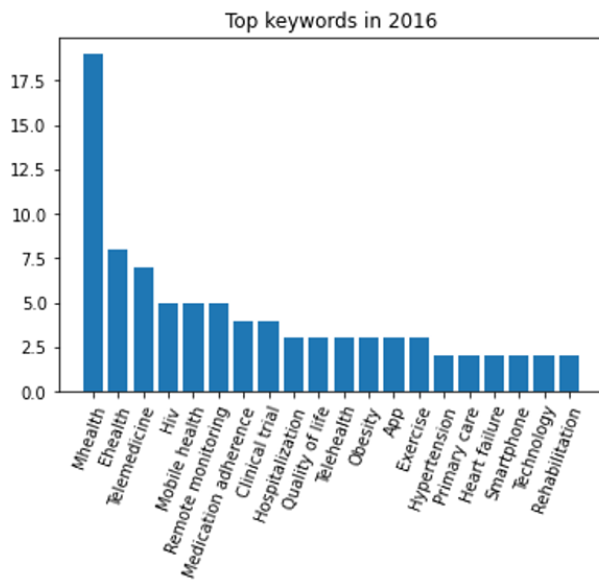
Table 2. Top Terms Associated with Digital Health

Top “Digital Health” Key Words	
Mhealth	206
Ehealth	108
Mobile health	95
Telemedicine	82
Digital health	51
Telehealth	25
E-health	18
M-health	11

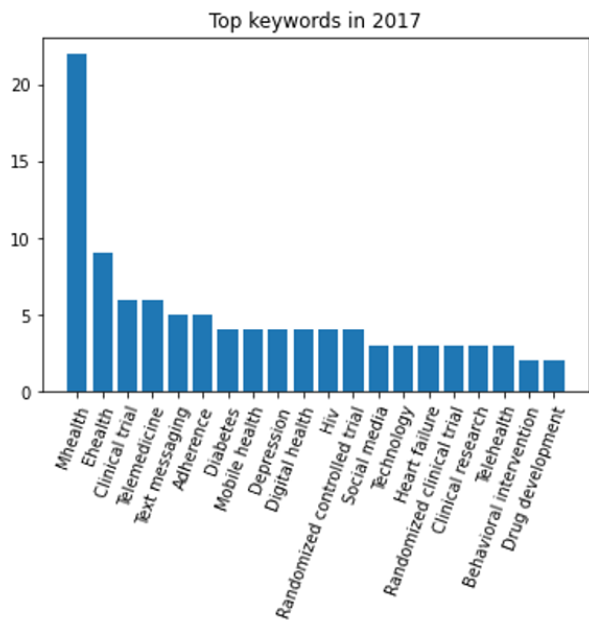
The usage of these terms has varied across the last few years but the dominance of ‘mhealth’ or mobile health technologies had remained consistent as seen in Figure 5. The number of studies featuring ‘mhealth’ doubled from 2016 to 2018 as interest in digital health grew. Furthermore, in 2017, the FDA finally addressed digital health in a major move by creating a Digital Health Action Plan. This signal by the FDA welcoming innovation in healthcare likely encouraged growth in an emerging field. Critically the change in top keywords demonstrate the developing interest in digital health as new technological advances enter the consumer market and there is a drive to validate these technologies. The prevalence of ‘randomized controlled trial’ in abstract is almost quadrupled in 2020 compared to 2017. Although many studies were protocols or pilots for future full length clinical trials, there clearly is greater interest in exploring digital health through rigorous, randomized controlled trials.

Figure 4. Top Keywords from Digital Health Studies from 2016-2020

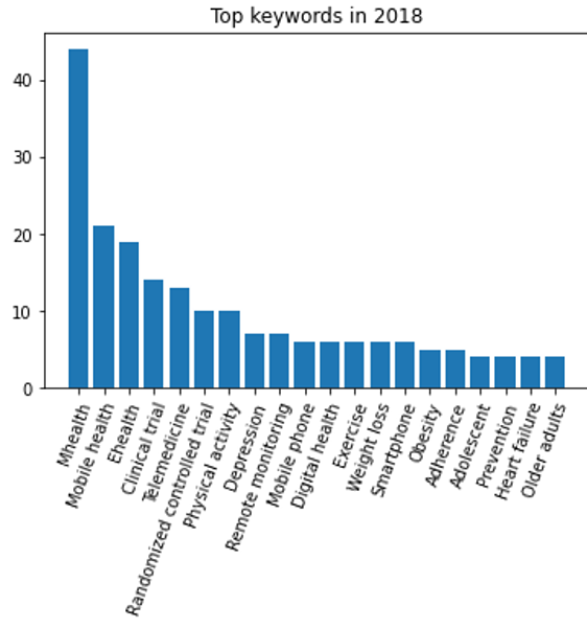
a. Top Digital Health Related Keywords in 2016



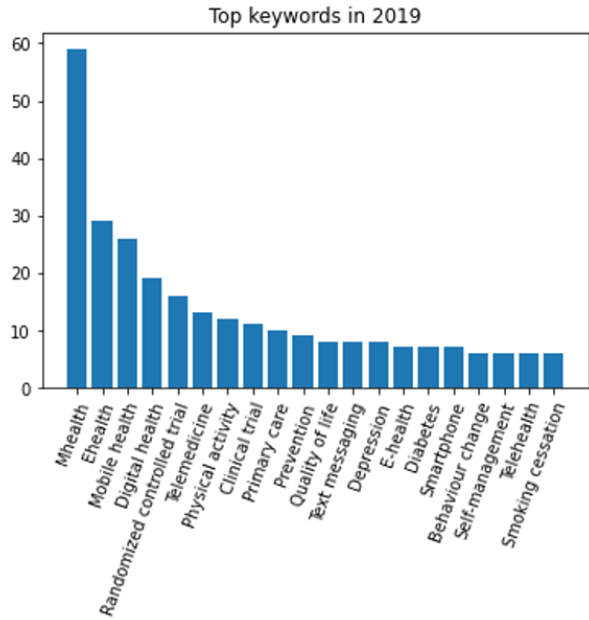
b. Top Digital Health Related Keywords in 2017



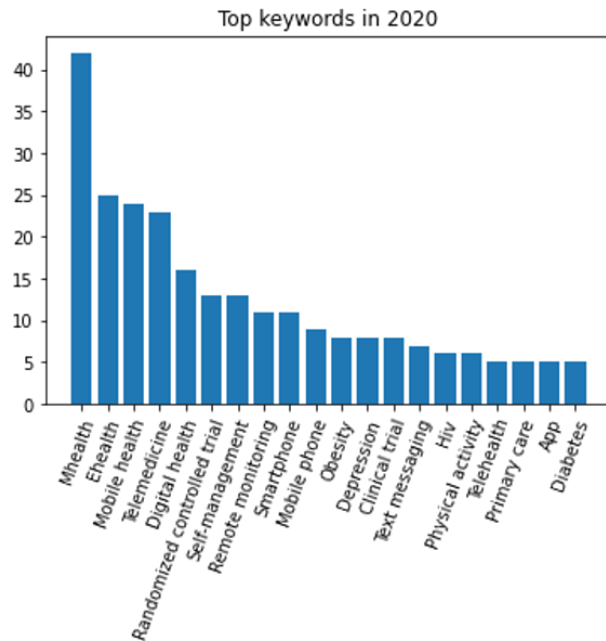
c. Top Digital Health Related Keywords in 2018



d. Top Digital Health Related Keywords in 2019



e. Top Digital Health Related Keywords in 2020



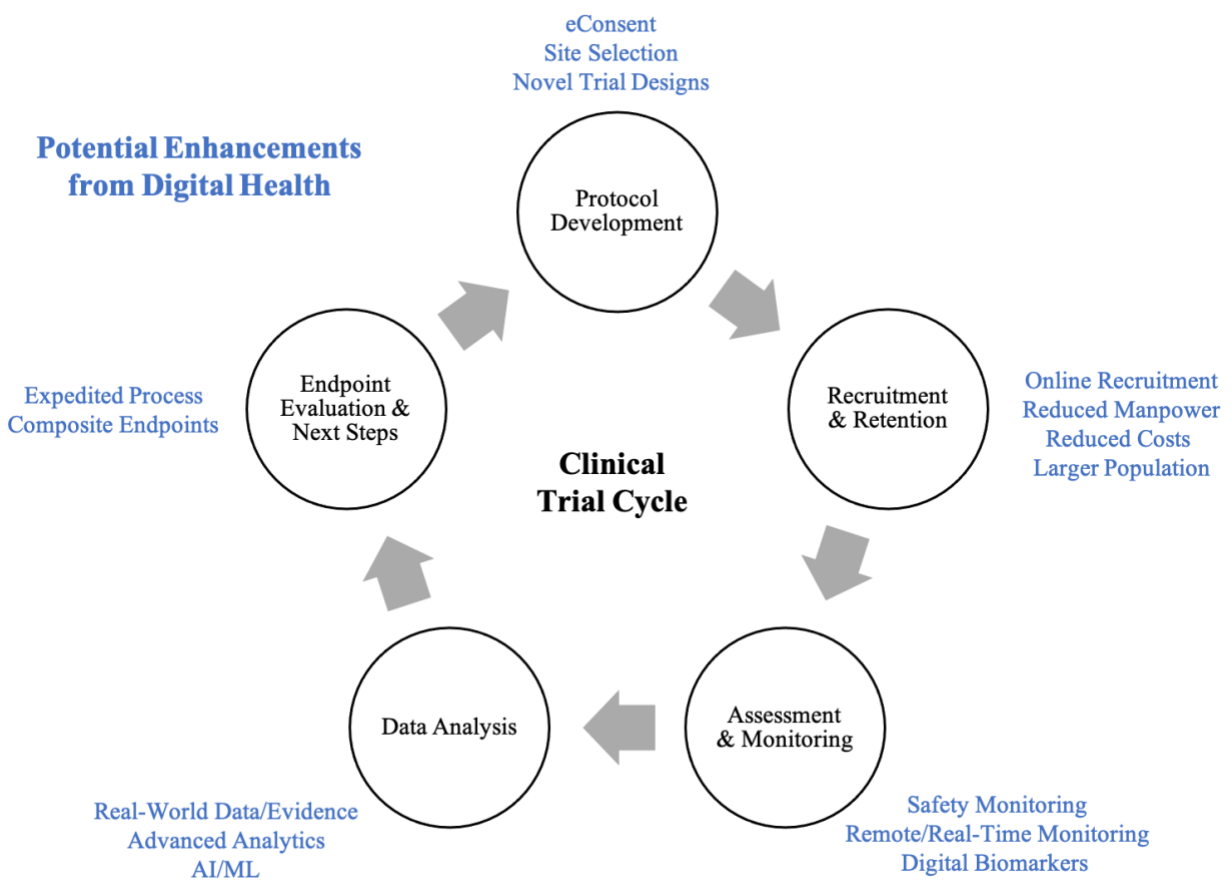
The implementation of digital health across therapeutic areas is inconsistent as seen in Figure 6.

The most popular category, Cardiovascular, is an expansive category that includes cardiometabolic interventions hypertension to remote monitoring through CIEDs and wearables.

The Potential Future of Digital Health in Clinical Trials

There is numerous ways digital health can be implemented into the current clinical trial process that will not only improve current methods but also create new models for future trials (Figure 6). From the initial protocol development, digital health can play a critical role before patients are even selected.

Figure 6. Digital Health Applications in Clinical Trials



Recruitment of patients through social media or health related forums provides access to a larger study population and may provide access to a younger target population that would have otherwise been difficult to contact and recruit into a medical study. Many clinical trials lack generalizability because of a failure to recruit diverse patient samples during the clinical trial and

many trials do not even report race or ethnic data (Geller et al., 2018). As a result, data for underrepresented racial and minority populations often comes from post-market studies after regulatory approval. Recruitment through social media can address issues of diversity by appealing to a larger population. Furthermore, retention in digital clinical trials has the potential to be much higher with the use of digital technology. The aforementioned minority populations may be hesitant to participate in clinical trials because of barriers from transportation and lost wage from missing work. A digital trial would cater to their schedule and allow the patient to participate and engage on their own time. This would improve the diversity of patients included in clinical research.

Clinical trial language is often confusing to participants who may not fully understand the requirements before they decide to participate. This lack of understanding can result in a failure to follow the protocol or drop-out, both of which can negatively impact the success of a trial, regardless of the effectiveness of the treatment. Digital technologies can assist in addressing these issues by providing better communication and easing the barriers to participate in a clinical trial. Patients could electronically provide consent and watch pre-recorded videos that clearly state the requirements of the clinical trial. From the investigator or sponsor perspective, a digital clinical trial may be easier to manage. Previously, an investigator would be tied to the specific clinic or site to conduct the clinical trial but through digital technologies, investigators could be monitoring patients from any location. No longer restricted geographically, investigators could manage more patients and spend more time on decision making for treatment than logistical considerations. However, as clinical trials move to become more digital, the digital divide between those who have access to WIFI and those who do not, grows. This division exists for

those who do not have a mobile phone, smartphone, computer, etc. and can continue to the point that lacking such devices can greatly impact an individual's health outcomes.

Digital endpoints, data generated from digital devices such as smartphones or wearables, are poised to radically change the way treatment can be delivered and personalized for each patient. By collecting data from an individual's everyday life, investigators can have an in-depth understanding of the individual's behavior and how their disease affects them. Critically, digital endpoints may provide sensitive measures of change in a patient's health that previous measures could not capture. Although patient-reported outcomes are essential to many trials, digital devices can capture objective data minimizing possible recollection bias from patients. As these technologies mature, the flow of a patient's data to the investigator could become a dynamic process. Adverse events are of great concern to investigators during a clinical trial because they could signal serious issues with the treatment of interest. With real-time data from patients, investigators could almost instantaneously respond to adverse events or possibly predict future events based on the data. This is the greatest potential of digital health that is yet to be explored where real-world data is analyzed in real-time with machine learning or complex algorithms to make critical decisions around treatment as more data is received. The clinical trial evolves beyond testing a treatment in a patient but becomes an interactive and dynamic process where decisions are made in real-time to thoroughly explore the effects of a treatment in a patient. Digital health may also increase the ability to perform Bayesian clinical trials that rely on continual updating of observed data to make decisions. Real-time data collection enables the Bayesian posterior distribution to reflect the most current belief about the treatment effect and enables decisions regarding study termination for efficacy or futility to be made sooner, potentially reducing the number of patients required and the overall cost of the study. While

moving towards digital health technologies can increase the size of trial populations, reduce the burden of running a single trial on investigators, and provide novel measurements, there is a significant shift of responsibility towards the later stages of a clinical trial. Data cleaning, processing, and analysis will become exponentially more complex as a single patient could have hundreds of thousands of data points, most of which are accurate and relevant. The burden to analyze these data points into meaningful conclusions will fall on biostatisticians and the new emerging class of analysts, data scientists.

Digital health is always evolving and could also play a role in platform trials, a new form of clinical trials. Platform trials have a flexible design that allows investigators to run multiple interventions and add or drop different arms as the trial proceeds based on data from interim analyses. The platform trial is not only an effective trial design when multiple therapies exist but also provides an ethical solution. During the Ebola crisis, a platform trial designed was deployed to evaluate multiple treatments and ineffective treatment arms were quickly removed without needing to stop the entire trial or waiting for pre-specified outcome measures (Thielman et al., 2016). Digital health has much to offer to platform trials by providing real-time data that could better inform decisions to drop or add treatment arms. Interim analyses could be performed at more regular intervals and ease the process of onboarding of patients to a new treatment arm. With the COVID-19 pandemic, it quickly became clear that digital devices could be used to supplement or replace critical infrastructure, such as hospitalization or clinic visits.

A major touted benefit of digital health is the large amount of more accurate and useful data that can be collected to make informed decisions about an individual's health. These assumptions raise critical issues around the reliability of digital health devices and what is useful data. Collected data may not always be accurate and could pose serious health risks should

treatment decision be made on inconclusive data. Furthermore, digital health may only exacerbate existing issues with data dredging. In recent years, the scientific community has been under increasing scrutiny for fabricating, exaggerating, and selectively omitting data resulting in the current replication crisis that many scientific studies are impossible to reproduce or replicate (Ioannidis, 2005). Data from digital health devices may overwhelm investigators and tacticians with meaningless data and result in attempts to find meaningful trends or patterns that may not exist. Clinical trials are extraordinarily costly and the pressure to find statistically significant results could increase p-hacking or other data manipulation techniques (Adda et al., 2020). Digital health also cannot address fundamental issues that arise from data collection such as sparse data bias (Greenland et al., 2016). Regardless of the total sample size, combinations of certain observations and risk factors can result in insufficient data that does not support estimates which results in this bias. Digital health may only increase the total data but cannot supplement data that does not exist because of lack of diversity in a study population. This enormous amount of data can also become a major burden the patient and clinician.

[The Evolving Regulations Around Digital Health](#)

With technological advancements and increasing accessibility of digital devices and tools, the need for regulatory oversight to ensure highly quality healthcare is critical. Although the healthcare industry has been notoriously slow at adopting new technologies, the prevalence of mobile devices and low barriers to developing mobile applications or software has caused the health technology sector to set record funding numbers in the last few years (Safi et al., 2018; Chiu et al., 2020). Organizations or individuals with no health-related background but have strong computer science abilities, are entering into a market that is predicted to be worth \$639.4 Bn by 2026 (PR Newswire, 2020). However, there are serious concerns about the risks

associated with unchecked digital tools that at best provide no benefits and at worst cause undue harm to users. Furthermore, digital devices could result in overutilization of healthcare resources when patients who do not need assistance seek medical care because they are acting on erroneous data from their device (Wyatt et al., 2020). Regulatory oversight is needed to ensure data quality, validation of devices, interoperability, data privacy, and evaluating effectiveness of devices on tangible health outcomes. Moreover, as we enter into an era of big data, the health informatics problem of what to do with an overwhelming amount of relevant or irrelevant data must be addressed. The U.S. Food and Drug Administration (FDA) has regulatory oversight of digital health because of their consideration as medical devices to some extent through the Center of Devices and Radiological Health (CDRH). However, as digital health is applied to aspects of health and science in innovative methods, regulation of these technologies becomes unclear. To this point, stakeholders have continuously criticized the FDA for its slow regulatory process which they claim hinders innovation, especially for smaller companies and the FDA's traditional approach to medical devices and technology is inadequate.

In late September 2020, the CDRH launched the Digital Health Center of Excellence (DHCoE) to "align and coordinate digital health work across the FDA" (FDA, 2020b). The DHCoE is a major development from the FDA to address the growing digital health sector. It is the beginning of the FDA's attempt to comprehensively address digital health with a focus on allowing innovation and advancement by working with selected partners. The DHCoE will cover mobile medical devices, artificial intelligence and machine learning (AI/ML), software as a medical device (SaMD), and wearables (FDA, 2020d). Rather than acting as an authoritative body, the DHCoE will instead function to provide regulatory advice and support to the FDA's regulatory review and assist in setting research priorities for the CDRH (FDA, 2020b). Critically, the

DHCoE will not be responsible for making marketing authorization decision (FDA, 2020b). This advisory role of the DHCoE is clearly demonstrated though its stated goals to “empower digital health stakeholders to advance healthcare by fostering responsible and high-quality digital health innovation” across nine functional areas (FDA, 2020b).

Data security and privacy issues are one the greatest challenges to digital health adoption. In the US, HIPAA, the Health Insurance Portability and Accountability Act and later 2009 amendment, set the standards for health privacy. HIPAA has fallen under increasing criticism for its entity-based privacy protections that only applies to covered entities, health plans and healthcare providers, and business associates, those performing services for covered entities. This narrow scope fails to include developers of digital health devices such as mobile apps that collect sensitive personal health data. The range of apps that collect health data not protected under HIPAA range from general wellness apps to mental health or fertility tracking apps, all of which include extremely sensitive data. Often times, the apps themselves offer little information about their privacy policies or data security (O’Loughlin et al., 2019). In contrast to HIPAA, the European General Data Protection Regulation (GDPR) and California Consumer Privacy Act focus on centering protection arounds the data itself rather than entities who use it (Bari, O’Neill, 2019).

A critical and still developing aspect of digital health is artificial intelligence or machine learning (AI/ML). The potential of AI/ML to generate new insights into diseases based on real-world data and offer novel solutions that could be personalized, is unmeasurable. These technologies are able to monitor real-time performance and continuously analyze data for ways to improve health care for patients (FDA, 2021). This type of digital health is yet to be thoroughly explored in

clinical trials but the potential in AI/ML is limitless. However, AI/ML faces unique regulatory barriers as numerous questions around data privacy, potential for harm, and data validation exist. SaMD exemplifies the complexities of regulating digital health because of its broad range, iterative, and innovative nature. SaMD can take the form of software that determines the proper drug dosage for patients or software that detect and diagnoses diseases. It is a dynamic device whose risk can vary widely. Digital therapeutics (DTx) is one prominent category of devices that fulfill the definition of SaMD (Digital Therapeutics Alliance, n.d.). This software can deliver evidence-based therapeutic interventions that assist patients in the prevention, management, and treatment of numerous diseases. Digital therapeutics can increase patient access to novel treatments that traditional therapies were unable to address. The varied forms that SaMD can take presents a unique challenge. The FDA recently approved the first game-based digital therapeutic, EndeavorRx, through the de novo pathway, a regulatory process for novel medical devices, based on data from five clinical studies (Akili Interactive, 2020a). In the prospective randomized controlled study, EndeavorRx demonstrated improved objectively measured inattention in attention-deficit/hyperactivity disorder (ADHD) pediatric patients with minimal adverse events (Kollins et al., 2020). Since its approval, data from its multi-site open-label study investigating the impact of the intervention on the daily life, has found early exploratory evidence that following treatment, children had improved math and reading skills (Akili Interactive, 2020b).

Another illustration of SaMD can be found in artificial intelligence and machine learning (AI/ML). The potential of AI/ML to generate new insights into diseases based on real-world data and offer novel solutions that could be personalized, is unmeasurable. These technologies are

able to monitor real-time performance and continuously analyze data for ways to improve health care for patients (FDA, 2021).

Digital Health Software Precertification Program (Pre-Cert) that was launched as a part of the Digital Health Innovation Action Plan from the CDHR in 2017 (FDA, n.d. innovation action plan). Reimagining digital health product oversight materialized in the formation of Pre-Cert. This program was designed to allow for faster review of medical devices and reduce the number of submissions the FDA receives. These goals would be achieved by “pre-certifying” certain digital health developers who demonstrated “a culture of quality and organizational excellence based on objective criteria” (FDA, n.d.a). Those who are pre-certified could then market their low-risk devices without additional FDA review or could receive a streamlined review (FDA, 2020a).

Participating developers could potentially have their real-world data be used to support the devices regulatory status and provide further evidence of its safety and effectiveness. Pre-Cert 1.0 officially began in 2019 and selected nine partners: Apple, Fitbit, Johnson & Johnson, Pear Therapeutics, Phosphorus, Roche, Samsung, Tidepool, and Verily (Google) (FDA, n.d.d). One of the partners in the program, Pear Therapeutics, is a prescription digital therapeutic developer who has already gone through the FDA approval process for one of its digital therapeutics. reSET, which helps treat patients with substance use disorder, was approved in 2017 under the De Novo pathway after it demonstrated improved abstinence and treatment retention in clinical studies (Pear Therapeutics, 2017).

However, the FDA’s traditional framework for regulation falls short for devices that constantly adapt and change. The FDA has approved a so-called “locked” AI/ML-based SaMD but the true potential of these devices lies in “learned” algorithms. Locked algorithms cannot evolve based on new data received and remain in a frozen but tested and verified state. However, for AI/ML-

based SaMD, continual innovation utilizing received data is core to the function of the device but this innovation can threaten its own regulatory approval. To address these issues, in 2019, the FDA proposed a regulatory framework for premarket review of AI/ML-driven software modifications (FDA, n.d.c). This framework, the total product lifecycle approach is based on the precertification program which accounts for rapid innovation and “learned” or adaptive AI/ML algorithms. However, the process for approval and implementation is still murky at best because of the complex challenges AI/ML poses to regulatory oversight. Even prior to undergoing regulatory approval, how does the FDA decide if an AI/ML-based SaMD produce needs approval? Once a device is approved, given its iterative nature, how does the FDA ensure that device remains safe and effective for patients over time? Will all iterations require FDA approval and how is the risk associated with different iterations? Clearly, these are serious concerns that will only continue to grow as technology advances. Some have suggested that the FDA should take a system approach, rather than a product approach, because AI/ML-based SaMD are highly dynamic and are heavily influenced by the environment and external factors (Gerke et al, 2020). However, a system’s approach would require the FDA to consider information outside of its normal purview and may go beyond its legal authority. Information on reimbursement from insurers, data usage, data quality, social behavioral biases, interoperability would greatly improve the ability for the FDA to regulate AI/ML-based SaMD but place an enormous burden on the FDA (Gerke et al, 2020). Recent controversy on twitter’s alleged racist AI, where the algorithm chooses to display light-skinned individuals in thumbnails over dark-skinned individuals, highlights how AI/ML could further introduce racism into healthcare. Should these social considerations be ignored, AI/ML-based SaMD could perpetuate and re-enforce racist

perceptions and further health inequities in a system struggling to establish trust in minority communities because the underlying data which trained the algorithms is biased.

The COVID-19 pandemic has greatly accelerated the FDA's response to digital health use in clinical trials. According to Marra et al (2020), prior to the pandemic, almost 1200 clinical trials incorporated a digital health device and once the pandemic began to disrupt trial processes many investigators turned to digital health tools from remote patient monitoring to telehealth to ensure the trial could proceed without comprising patient safety. In response to the pandemic and to minimize its disruption, the FDA issued a guidance document on how trial sponsors could continue their operations. This sudden shift to utilizing digital health devices for many clinical trials will provide much insight from investigators and study participants to the FDA on how it will approach future regulatory guidance.

Conclusion

Interest in digital health has exploded in the past few years with an exponential increase in the number of articles on digital health. Furthermore, this interest has expanded beyond applying known digital health solutions to new therapeutic areas to creating and tailoring devices specifically for certain diseases and indications. While certain devices, such as a mobile app, can have universal application and utility, truly successful digital health devices are likely to be specifically tailored and designed for their targeted disease.

As digital health enters into a mature phase, current prominent therapeutic areas such as diabetes and cardiovascular disease will become saturated with common digital health devices. True digital health maturity will manifest as uniquely designed devices specific for its indication. However, prior to this maturation, general application of digital health devices is common because of their wide utility. As such, many see clinical trials to be a prime venue to utilize the

potential benefits of digital health. Digital health can not only reduce costs and patient burden but also introduce novel methods of data collection and data analysis. The true value of digital health in clinical trials has yet to be fully explored but should not be underestimated.

Limitations

There were a number of limitations in this literature review. While the PubMed search was broad and included a number of digital health related keywords, it is likely that some digital health technologies or devices were not included because the language used in digital health is still evolving. Although PubMed is an extensive database of biomedical literature, digital health devices and solutions exist outside of this literature and may not be rigorously tested and published in journals. A number of grey literature articles were included to supplement potential gaps but some digital health technologies not yet published were likely not included. Many clinical trials do not publish their findings in peer reviewed journals and thus this analysis would under count the total number of digital health clinical trials. Furthermore, stakeholders may already be utilizing digital health technologies in their clinical trials but have not made that information public. An assumption was made that the number of published articles in PubMed is correlated with digital health interest and growth. However, a number of potential delays such as the article review process could have delayed publications to a later year.

Future Directions

This thesis broadly explored the digital health landscape including all potential devices across all therapeutic categories. Future research could investigate the application of a specific digital health device in a therapeutic area and the benefits of said device. With more and more clinical trials including some digital health component, there is still much to be explored about how digital health can assist in expanding beyond traditional clinical trials.

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