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著者(和文)	小野寺玲子
Author(English)	Reiko Onodera
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REIKO ONODERA

Graduate School of Innovation Management

Tokyo Institute of Technology

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ABSTRACT

The purpose of this thesis is to explore how mobile health (hereafter mHealth) innovation affects existing medical systems, investigate the mHealth innovation process, and examine the relationship between the diffusion of innovation in advanced technology and the relevant regulations. mHealth falls within digital health, an interdisciplinary area encompassing medicine and ICT, and is particularly expected to revolutionize the medical field as it grows in market size. Through this thesis, I seek to provide a deeper understanding of the role of mHealth and clarify the factors that cause changes in the healthcare industry. Exploring the factors behind the diffusion of advanced technology innovation and its impact on industrial structures will provide important knowledge for realizing efficient and high-quality medical care.

As background information, the first chapter, "Introduction" describes the current situation of the healthcare industry and presents a literature review of previous works done on mHealth. Based on these works, I created a theoretical framework based on the 4Ps of innovation space, developed by Tidd and Bessant in 2005, to explore how mHealth innovation affects existing medical systems as an example of ICT in healthcare. The chapter concludes with a remark that the thesis aims to reflect on the special characteristics of this regulated industry, upon which social security systems depend, and investigate mHealth based on the 4Ps of innovation space.

The second chapter, "Exploring the potential of mHealth as product and process innovation for healthcare" aims to examine mHealth from the product and process innovation perspective. For this, I utilized data from ClinicalTrials.gov, a database of clinical trials in the US, to investigate the development status of mHealth regarding pharmaceuticals and medical equipment and analyzed the findings through well-established innovation theories, specifically concerning innovation process, types, and dynamics aspects. Data from clinical trials were used for this because they are mandatory for all new medical inventions, and thus, represent innovation in healthcare better. The results showed that mHealth is only applied to a limited number of purposes and diseases. Currently, its main application is in the promotion of patient compliance through pre-existing devices and services, which was found to still be in its infancy where the development of various services utilizing cutting-edge information and communication technologies is concerned. The chapter builds on these findings and discusses the diversification of supported diseases and participating enterprises, the support and substitution

from pharmaceutical businesses, and collaborative developments with cutting-edge technologies as keys to advancing mHealth.

The third chapter, “Innovation process of mHealth: An overview of FDA-approved mobile medical applications” analyzes the approval of mHealth solutions based on the medical front of the 189 FDA-approved mHealth products since 2016. The chapter also aims to pinpoint important factors for creating a market for mHealth based on positional innovation. The analysis found that current mHealth products differentiate themselves from their conventional counterparts, such as preexisting medical equipment, through miniaturization and wireless capabilities and that only 18 products were found to develop new markets based on cutting-edge technologies. In addition, forerunners in the mHealth market were found to be ICT companies and startups, not preexisting medical equipment manufacturers or pharmaceutical companies. Moreover, products that develop new markets based on cutting-edge technologies were found to be developed by US-based companies established on or after 2001. These companies were found to provide added value to existing products by supplying preexisting players in the healthcare industry with mHealth as a supplementary asset. The chapter discusses the possibility that the aforementioned ICT and startup companies may grow into platform leaders in future markets. Furthermore, the chapter examines how regulations may influence the growth of the mHealth market and refers to the possibility that in mHealth, the clarification of policies and regulatory conditions may have encouraged enterprises to enter the market.

The fourth chapter, “The impact of mHealth on existing medical systems” describes mHealth innovation from the paradigm innovation perspective to clarify the impact of existing healthcare, especially for tension relationships among stakeholders, on quality, cost, and access of medical care. Based on my survey on mHealth in the United States, explained in chapter 2 and 3, I focused on the interaction between regulation and innovation in terms of the existing pharmaceutical and medical device industries. The maintenance of an appropriate balance between regulation and industry innovation, and the methods used to realize the purpose of regulations change with the advancement of technology. It is thus necessary to discuss regulations that reflect changes in the structure of society and industry. The aforementioned relationship between regulation and industry innovation was investigated through interviews and paradigm innovation in mHealth was considered based on the facts of this relationship. As a result, I identified the FDA and “medical entrepreneurs” as innovators driving changes in mHealth. The FDA has adopted an “interactive regulator” mindset in order to

adapt to the digital health field, and medical entrepreneurs and their companies have developed new markets by fusing innovative technologies with medical needs.

The fifth chapter, “Conclusions” discusses the main findings of the thesis, its contributions to existing research on mHealth, and the relationship between innovation and regulation. Furthermore, the chapter describes academic and practical contributions of my thesis.

CHAPTER 1. INTRODUCTION

1.1. Background

The healthcare industry has experienced a proliferation of innovations focused on developing diagnostic and medical treatment technologies, improving the quality of life, and augmenting the efficiency and cost-effectiveness of healthcare systems [1] [2]. Health systems must constantly innovate. First, they must respond to changing disease burdens and social environments. The objective of medical treatment is not only to help patients in need, but to maintain or improve people's overall health, including preventing illnesses [3]. Responses to unmet medical needs, where disease structures are concerned, are important. In the modern day, due to population aging, changes in disease structures, increases in the speed of treatment, and increases in healthcare costs, mainly in developed countries, is unavoidable [4]. Due to complications in drug discovery targets, the increased speed of drug discovery technologies, stricter approval reviews in the pharmaceutical industry, increases in research and development costs at pharmaceutical companies, and the improvement of productivity have become urgent issues [5].

Second, health systems must respond to technology with new ways of diagnosing and treating patients, offering cures for conditions that were once rapidly fatal or at least, as commonly seen, transforming such diseases into long-term disorders [2]. In the medical industry, even though such technology can improve the quality of medical care, help to overcome and contain illnesses, as well as help to develop a healthy society, there is still the possibility that it will be expensive to introduce, which may lower its efficiency. Thus, having both good quality healthcare and ensuring its efficiency is key. Additionally, there is a current focus on the move towards blending healthcare and ICT to improve the quality of healthcare, reduce medical costs, prevent medical errors, and reduce the management costs of medical data. Christensen (2009) states that, in addition to bringing about a change in the healthcare business model, ICT will fulfil two important and disruptive roles [6]. The first is making office work more efficient by promoting cooperation between healthcare providers and the computerization of medical information, such as medical records. The second is the potential of supporting cooperation between doctors, nurses, and patients, and transitioning healthcare to a network-style business at medical examination locations by overcoming time and space restrictions with the development of technology that is faster and has a large capacity.

There has been a notable change every 10 years in the history of computing. In the 1960s, mainframes were independent, but after the mini/micro-computers of

the 1970s, personal computers (PCs) became mainstream. After the so-called internet revolution of the 1990s, there was a transition to desktop PCs that connected to the internet before moving on to mobile devices in the 2000s. In addition, since 2010, wearable devices have begun to spread in earnest. Among these, a particularly remarkable phenomenon has been that of smartphones. The number of smartphone users has risen and now accounts for 30% of all mobile phone users (around 5.2 billion people) globally [7]; previous predictions had suggested that this number would have risen to 30% of the global population by 2018 [8]. Moreover, a survey's results have shown that smartphone users spend more time on their smartphones than they do watching television [9], and this usage time is beginning to overshadow other media.

Amid this trend, attempting to use mobile devices (such as smartphones) in healthcare, nursing, and public hygiene can be said to be a necessity. This is termed mobile health, or mHealth, and patient monitoring devices, personal digital assistants (PDAs), and wireless devices used for this purpose are expected to emerge [10]. In 2011, under the Obama administration, the United States' Department of Health & Human Services recognized mHealth as one of the most important breakthrough technologies of current times [11]. During the same period, the WHO commented that mHealth describes a new horizon in healthcare and health using mobile technology [12]. There are three factors backing mHealth [13]. One is the realization of two-way, high-quality communication by increasing transmission and processing speeds and memory capacity. The second is the appeal to decrease costs given the increasing burden of healthcare and nursing costs on the public. The third and last reason is the importance of offering faster, more accurate, and more individualized healthcare/nursing services. If this trend were to continue, from around 2017, the mHealth-related market size of approximately $21.1 billion could be predicted to grow by an average of 33.7% each year in future, reaching a value of $90.4 billion in 2022 [14]. Furthermore, while the market segmentation is dominated by Europe, Asia, and North America, it is presumed to expand to the entire world [14,15]. In a prediction of mHealth's fields of application, patient monitoring usage is the largest at approximately 65%. The areas predicted to be targeted by this are blood glucose concentration, blood pressure, pulse oximetry, sensory perception/mental condition, sleep apnea syndrome and sleeping condition, and fitness/heart rate, in addition to other personalized applications [16].

Healthcare ICT is developing rapidly, especially in the United States. In 2017, 64% of people were using digital devices for health management, forming the base of healthcare ICT [17]. With the development of devices and the internet of

things (hereafter IoT) technology, various kinds of healthcare and health data are generated and accumulated every day. However, the real focus is on artificial intelligence (AI). In the field of healthcare, in 1973, AI incorporating rules based on the knowledge of experts succeeded in finding blood disorders from blood test results and prescribing antibiotics [18]. The use of this rule-based AI was limited, but recently, there has been an improvement in image recognition technology using deep learning, which is thought to bring about a revolution in healthcare [19]. In 2014, in a collaborative research with the Memorial Sloan Kettering Cancer Center, IBM developed a technology that can diagnose skin cancer faster and more accurately than conventional methods: detecting melanoma with a 95% degree of accuracy [20]. In addition, concerning diabetic retinal disease, IBM used deep learning and visual analysis technology, and announced a method of diagnosis that categorizes the degree of severity of the patient's symptoms with an 86% degree of accuracy [21]. On the medical front, digitalization is rapidly progressing, with systems being introduced that generate and use a large amount and wide variety of data, including numerous tests and image data. There is an emerging trend in which data are created and accumulated daily [22].

In healthcare, upon conducting calculated trials, it is important to improve the degree of accuracy in determining and diagnosing illnesses. mHealth can contribute in this regard. Before mHealth, measuring locations were limited to medical institutions, and even if data were acquired, there were issues such the length of time it took to analyze the data. However, with developments in technology, it has become possible to make methods mobile and wearable, and to allow real-time data to be collected and accumulated less expensively. In addition, with transmission having been sped up, it has become possible to send and receive a large volume of data. Due to the development of cloud services, it is also becoming possible to share medical information quickly and safely. With advanced technology such as this and wearable devices being adopted by mHealth, the costs and degree of invasiveness of collecting biological information are greatly reduced. Moreover, if this information is collected or combined with other biological data (such as genome and medical checkup information, otherwise known as big data—a collection of data including both structured and non-structured, that is so large that conventional database management tools are insufficient to handle it) and analyzed by an AI representative of machine learning, we can expect it to create new value that had previously not been possible. An extreme application of this is individualized healthcare: offering advice to optimize disease countermeasures, promote good health, and prevent disease for each individual person or patient.

This thesis focuses on mHealth, which is considered a form of innovation in healthcare predicted to grow in the market, even within the area of digital health (an area where healthcare and ICT merge).

1.2. Previous literature of mHealth

1.2.1. Historical transition of mHealth

mHealth is an emerging concept relating to the use of mobile devices and wireless technology for healthcare purposes. mHealth is a branch of Electronic Health (hereafter eHealth) [23]. The term eHealth is defined as “healthcare practices assisted by communication systems and electronic process." [23]. The term mHealth is broadly defined as “the use of mobile and wireless devices to improve health outcomes, healthcare services, and health research” [10]. The technologies used for mHealth include text messaging, phone call services, mobile tracking devices, wearable sensors (which can used for monitoring and measuring activities), applications (apps) and wireless communications technologies among others. The scope of mHealth extends to acquisitions and transmission of healthcare-related information, telemedicine, electronic record keeping, e-prescribing, and parallel industries such as fitness and wellness [23].

The diffusion of mobile phones and smartphone technologies is making it possible to expand the applicability of mHealth [24]. Today, mobile phones and smartphones have become essential parts of our lives. Smartphones have been defined as “mobile telephones with computer features that may enable them to interact with computerized systems, send e-mails, and access the web” [25]. In 2014, the number of mobile phone users reached 5.2 billion, with a population penetration of 73% [26]. As for smartphone users, their number was predicted to surpass 2 billion worldwide by 2016 [27]. The healthcare and life sciences sectors are said to be two of the top three fields likely to experience new mobile business model growth in the next five years [28].

The healthcare and life sciences sectors are said to be two of the top three fields likely to experience new mobile business model growth in the next five years [28], not only in using mobile phones and smartphones, but also in using a wide variety of wearable biometric sensors such as watches, bracelets, skin patches, headbands and earphones [29].” The terms “wearable devices” and “wearables” refer to electronic technologies or computers that are incorporated into items of clothing and accessories that can be comfortably worn on the body [30]. These wearable devices can perform many of the same computing tasks as mobile phones and laptop computers. In 2015, 72.1 million wearable devices were shipped (representing a

stark increase of 173.3% from the 26.4 million units shipped in 2014), as new vendors, including Apple, entered the market [31]. Shipment volumes were expected to experience a compound annual growth rate (CAGR) of 42.6% over a five-year forecast period, reaching 155.7 million units in 2019 [31].

Similarly, the field of mobile applications for mHealth, mHealth apps, is rapidly growing. The number of mHealth apps that are published on the two leading platforms, iOS and Android, has more than doubled in only 2.5 years to reach 165,000 apps by Q3 2015 [32]. The market revenue reached USD 2.4 billion in 2013 and was projected to have grown to USD 26 billion by the end of 2017 [33]. Currently, the majority of mHealth apps have simple functionality only, and are used mostly for prevention and wellness [34].

The global healthcare IT market is projected to reach USD 66 billion in 2020, driven by efforts to streamline critical workflow processes [35], and mHealth is expected to be one of the driving forces of the global healthcare IT market [36]. The global mHealth market was valued at USD 10.5 billion in 2014 and is expected to have grown at a CAGR of 33.5% by 2020 [36]. In [36], it is reported that North America holds the largest market share, and based on device type, the blood pressure monitors segment holds a dominant share in the mHealth market, followed by blood glucose monitors and cardiac monitors as the number of patients with lifestyle-related diseases increases.

1.2.2. Previous literature review of mHealth

The number of mHealth-related publications is growing gradually from 2002. The majority of published evidence in support of its clinical use is limited to underpowered pilot data [37]. mHealth is an emerging medical field; however, it is expected to present a great potential for mHealth technologies to reengineer almost every facet of healthcare and, in the process, markedly improve our understanding of human physiology in health and disease [37].

mHealth could benefit ambulatory individuals in 2 general ways: (1) allow them to more easily and reliably self-diagnose their acute symptoms, and (2) enhance monitoring, tracking, and communication of various biometric information (e.g., blood pressure, glucose levels, spirometry values, oxygen saturation) for individuals with chronic medical conditions, enabling greater engagement and partnership in their care [38].

The widespread implementation of mHealth technologies, in their totality, can improve consumer convenience by potentially ensuring better control of chronic conditions and by allowing for more rapid diagnosis and treatment of common acute

conditions. Simultaneously, the number of unnecessary visits to physicians' offices and emergency departments potentially could be substantially decreased, reducing healthcare costs.

As I mentioned before, Christensen (2009) stated that ICT plays two important and disruptive roles in promoting changes in healthcare business models [6]. The first point is improving the efficiency of office work by promoting collaboration between medical providers and digitalization of medical information such as medical charts. The second point is to promote collaboration between physicians, nurses, and patients in clinical practice by overcoming temporal and spatial restrictions due to the development of high-speed / large-volume technology, and to shift medical care to network-type businesses.

It is important to build a doctor-patient relationship and nurse-patient relationship for delivering high-quality healthcare. Effective doctor-patient communication is a central clinical function and a central component in the delivery of healthcare [39]. Currently, the three main goals of doctor-patient communication are creating a good interpersonal relationship, facilitating the exchange of information, and including patients in decision making [40]. The relationship that is established between the nurse and the patient is essential for the delivery of quality nursing care [41]. In this context, communication involves more than the transmission of information; it also involves transmitting feelings, recognizing these feelings, and making the patients aware that their feelings have been recognized [42]. Historically, doctors and nurses were the sole providers of information about a patient's health; however, mHealth enables patients to "send" information about their health to nurses and doctors. In the near future, mHealth could help doctors and nurses to suggest personalized care to their patients through analytics and prediction functions and suggestions based on the collected real-time data.

In addition to communication, the usefulness of mHealth in each field is being studied. mHealth interventions, and recently published protocols [43-47] focus on the application of specific devices (e.g. mobile phones [48-52]) or specific functions (e.g. text messaging [53,54,55]) to individual diseases or healthcare fields (e.g. diabetes care or chronic disease management [30,54,56]); regulatory requirements on mHealth are also underway [57].

The usefulness of mHealth in clinical trials has also been studied. Recently, the pharmaceutical industry has struggled with high research and development (R&D) expenditure and high failure rates. The R&D activities of pharmaceutical industry are characterized by high levels of volatility because of long-term R&D periods, high costs, and demanding regulatory requirements with

low success rates [58]. Between 1996 and 2004 in USA, the average number of FDA-approved New Molecular Entities (NMEs) was 36 with an R&D spending of USD 65 billion per year [59]. In the period 2005–2010, the average number of approved NMEs was 22 but the R&D spending had climbed up to USD 125 billion [59]. The year 2014 saw the highest number of NMEs approved in a decade by USA and Japan, and was the biggest year to date for orphan-drug approvals in USA, EU, and Japan [60]. However, the cost of developing a new drug was estimated at USD 2.558 million in 2014 [61], while in 2003 it was USD 802 million [62]. One reason for these growing R&D costs is that drug manufacturers have been transitioning from small molecule drugs to biomedicines [63]. The pharmaceutical industry is trying to improve its productivity to substantially increase the number and quality of innovative, cost-effective new medicines, without incurring unsustainable R&D costs. Two recent systematic reviews [64,65] found modest and suggestive evidence for the benefits of mHealth technology, and while both reviews recommended implementation in clinical trials, they also argued that high quality (and adequately powered) clinical trials that measure clinical outcomes are essential.

In the field of therapy, WellDoc, Inc. developed BlueStar as a software application for guiding the treatment of Type 2 diabetes patients. BlueStar is the first application to achieve the trifecta of FDA-cleared, physician-prescribed, and payer-reimbursed digital medicine products [66]. Patients download BlueStar, prescribed by their doctors, to their smartphones and tablets. Patients' blood sugar levels are measured in real time and they receive individual guidance concerning the content of their treatment and their lifestyles from doctors and experts. The results of clinical trials showed improvement in hemoglobin A1c (HbA1c) scores over a 12-month period [67]. Moreover, WellDoc, Inc. has positioned BlueStar as a form of mobile prescription therapy (MPT) [68].

The Reset application developed by Pear Therapeutics was approved by the FDA to be used with outpatient therapy to treat alcohol, cocaine, marijuana, and stimulant substance use disorder (SUD). The Reset application provides patients with cognitive-behavioral therapy and helps them acquire skills to help treat SUD. It aims to increase abstinence from drug abuse and retention in outpatient treatment programs [69]. The data showed a statistically significant increase in adherence to alcohol, cocaine, marijuana, and stimulant SUD use by 40.3% and abstinence by 17.6% in patients who used resets compared with those who did not use them [70].

Meanwhile, the adaptation of mHealth to cognitive behavioral therapy for mental disorders is of a different nature. In this field, mHealth is expected to promote collaboration between doctors, nurses, and patients, and networking between patients and families. A number of new available apps are expected to help improve patients' conditions [71, 72]. However, in actuality, although several apps are commercially available for the treatment of and therapeutic support for mental disorders, a lack of evidence proving their effectiveness should be pointed out [72, 73]. In addition, there are signs of innovation resulting not only from technology push, but also from demand pull.

As described above, social expectations for mHealth are high and evidence-based clinical studies are increasing. However, research based on the viewpoint of technology management is not sufficiently done at present.

1.3. The relationship between innovation and regulation

Innovation is not simply the realization of new technologies; innovation is inevitably accompanied by changes in the social structure of society and the movement of people, things, and money the law has traditionally been prepared for [74]. For example, the growing prominence of platforms leaders [75] that offer new economic systems, such as the sharing economy, was not something the preexisting administrative framework (of top-to-bottom, business-by-business permissions, licensing, and supervision) was designed to contend with. We have arrived at a juncture where we must reconsider traditionally protected interests in a way that allows legislative regulations to promote innovation.

Such regulations include legislation itself, as well as administrative supervisory policies, guidelines, administrative interpretations, and the rules of self-regulatory organizations accumulated over time based on said regulations [74].

Regulation has a side that restricts innovation and causes a chilling effect [76], as well as causes opportunity loss. The maintenance of an appropriate balance between industry innovation and regulation, and the methods of realizing the purpose of regulations change with the progression of the technology of the age and society. Thus, it is necessary to discuss regulations that reflect the changes in the structure of society and industry [74,76-78].

On the other hand, the influences of regulation on corporate innovation are either positive according to the characteristics of various industries and companies [79], depending on the characteristics of technology [80]. For example, energy technology innovations resulted from policies that stimulate the adoption of widely available, but under-utilized, low-carbon technologies (including both energy

efficient and renewable energy technologies) and encourage the development and deployment of new near-term technologies that are close to achieving a market presence [81,82]. In the medical field, as an example of regulation contributing to the development of the industry, is the resolution to disseminate electronic medical records as an economic recovery measure to the "Lehman shock" by the Obama administration [83].

Technological innovation is conventionally seen as outpacing regulation, the latter being said to usually "lag behind" innovation [77]. We need a new framework to change "Innovation first/regulation after" to "co-development of the regulatory arena and novel technology" [77, 78]. New regulatory arrangements are seen as responses to the composition and material qualities of novel technologies and practices. In more commonsensical terms, furthermore, regulation is seen as surveilling, policing, approving or disapproving, and accrediting. Thus, regulation is not only seen as following innovation, but it is also seen as a socio-political force that is external to technological innovation and acts on it from a socio-political, non-technological realm of society [6].

A healthy relationship between regulation and innovation is important in healthcare industry. The intention of schemes to influence and regulate ground and air transportation, financial services, telecommunications, and healthcare industries in the public's interest evolves three stages [6]:

1. Subsidizing the foundation of industry
2. Stabilizing and strengthening the companies involved, ensuring fair and equal access to their products and services, and assuring that their products are safe and effective
3. Encouraging competition to reduce process

In the US medical industry, much of government regulation is now focused on ensuring the safety and effectiveness of suppliers and products. A key reason that changes in regulation consistently lag behind medical progress is that losses from the side destroyed by changes in regulations are large, so the regulations that were originally intended for patients are now for their own benefit. Regulations ultimately change in reaction to innovators' success in those markets; they rarely change to enable disruptive success [6]. For example, if we do not create a basic framework for regulation of entry, regulation of behavior, and supervision regimes in fields such as virtual currency and activities in space, we will have difficulties creating a necessary competitive environment and maintaining a sustainable business environment. This would result in the promotion of innovation through the creation of

legislative regulation, making them apt examples of how regulations made to suit the historical background of the situation can promote innovation [74].

1.4. Objective of the thesis

The aim of this research is to explore how mHealth innovation affects the existing medical system, examine the mHealth innovation process, explore the relationship between the diffusion of innovation in advanced technology, and examine the relevant regulations as an example of ICT in healthcare. mHealth belongs falls under digital health—an interdisciplinary area encompassing medicine and ICT—and is particularly expected to innovate the medical field and grow in terms of its market size. From the perspective of medical innovation, mHealth is to revolutionize patient care through a wide range of uses and regulatory authorities have begun to approve mobile medical applications. However, it is not clear what the key factor driving innovation is and how innovation is being created. Considering this situation, this study explores key factors that drive the growth of mHealth-related industry and potential innovation paths that corporate development strategies will adopt. I clarify the starting place in mHealth innovation and identify areas in need of an innovative approach for new models of care, changing professional roles, advances in communication, as well as data processing, increasingly being informed by evidence from healthcare. Not only is destructive innovation necessary for healthcare, but so is progressive understanding of innovation. Exploring the factors behind the diffusion of advanced technology innovation and its impact on industrial structure will form a body of knowledge for realizing efficient and high-quality medical care.

1.5. Theoretical framework of the thesis

1.5.1 The 4Ps of innovation

The purpose of the emerged theoretical framework is to work as the theoretical foundation for the following data collection and analysis. Furthermore, the theoretical framework will be used as the basis for satisfying the overall research purpose of providing a deeper understanding of the innovation process of mHealth. In this thesis, I referred to the 4Ps of innovation space [84,85] as tools to analyze mHealth innovation and the relationship between the diffusion of innovation in mHealth and regulations.

The 4Ps were introduced by Francis & Bessant (2005) as an approach to identify innovation types [84]. They suggested a diamond shape model to map innovation space that classifies innovation into four parts, each starting with the

letter “P,” thus collectively called the 4Ps of innovation. These are Product, Process, Position, and Paradigm [84]. Tidd, Bessant & Pavitt (2005) changed this shape into a circular model to show the degree of novelty of an innovation in addition to the 4Ps classification [85]. The mixture of the degree of novelty with the 4Ps of innovation resulted in a map of innovation space. Each of their 4Ps of innovation can take place along an axis running from incremental through to radical change; the area indicated by the circle is the potential innovation space within which an organization can operate. Whether the company explores and exploits all the space is a question of innovation strategy. As far as managing the innovation process is concerned, these differences are important. The model helps organizations identify where they currently have innovations and where they might move in the future. Another useful way to apply this concept is by comparing maps for different organizations competing in the same market, to determine where they might find innovation opportunities by looking at unexplored spaces.

The latter model was chosen since it helps us understand where we are and how we can innovate to improve products, processes, positions, and paradigms [86]. It gives us a direction of where we need to go, and in which areas of the business we need to innovate. The innovation space model supports the idea generation process and how a new idea can be incubated, as well as helps us identify relatively unexplored spaces that might offer significant innovation opportunities. Furthermore, this model includes not only the traditional categorization of innovation types, radical vs. incremental, but it includes 4Ps. If, say, emphasis has been placed on product and process innovation only, there may be scope for exploring position innovation— identifying new or underserved markets—or define a new paradigm—coming up with a new business model with which to approach the marketplace. We can also compare maps of different organizations competing in the same market and use the tool as a way of identifying relatively unexplored spaces which might offer significant innovation opportunities [87] [88]. We can use the model to look at where the industry currently has innovation, and where it might move in the future. An understanding of mHealth from the perspective of product, process, position, and paradigm is considered to lead to the arrangement of each stakeholder and the understanding of signs of change and tension. I also consider it a useful perspective to clarify the unique features of mHealth in healthcare. The 4Ps model is applied to explore potential innovation spaces, for example banking [89] [90], petrochemical company [91], and healthcare [2][92].

It is important to note the weaknesses of the model, however. The model does not clearly identify the boundaries between the innovation clusters or help companies identify the exact moment they move from one innovation cluster to another. This can indicate a weakness in the supporting dimensions, suggesting that further research is needed.

1.5.2 Designing the framework of this study

I designed an appropriate 4Ps innovation framework for my research to analyze mHealth in the healthcare industry. I defined the 4Ps and adapted these definitions to the purpose of this thesis as shown in Table 1-1, and I show the framework and concept based on previous and historical reviews of mHealth as depicted in Figure 1-1.

In the original definition, product innovation means "changes in the things (products and services) which an organization offers" [86]. Products and services for the patient as a consumer imply positive patient experience and improved health outcomes. For healthcare organizations, this can mean implementing product innovation into the delivery of patient care, from improving the methods of a clinical procedure to a new drug therapy to technology-aided patient experiences. Applying product innovation in mHealth can mean making changes in the products and services that an organization is developing for patient care delivery, for example, from improving the methods of a clinical procedure to developing a new therapy. For the purpose of this thesis, I defined product innovation as "changes in products and/or services with respect to technological novelty or fusion." The reason for this is that medical efficacy and safety are important when entering the field of existing medical devices and pharmaceuticals. A lack of mastery over existing medical devices, medicines, and other therapies is unacceptable for medical practitioners.

According to the original concept, process innovation refers to "changes in the ways in which they are created and delivered" [86]. The literature advises that "process management is mainly about optimization." Applying process innovation in mHealth can mean optimizing the processes of patient care delivery. One feature of mHealth is the elimination of temporal and spatial limitations. In addition, real-time patient data can be acquired, enabling healthcare professionals to understand the status of patients that had not been previously understood. In particular, mHealth is expected to contribute to the improvement of patient care in terms of data and communication. I defined process innovation as "changes in the ways that

clinical trials and medical delivery processes, specifically, are created and delivered."

In the original definition, position innovation means "changes in the context in which the products and services are introduced" [86]. From a business perspective, this means the position products or services within the marketplace. Applying position innovation in mHealth can mean segmenting the market by product or service novelty and using market novelty for positioning. I defined position innovation as "changes in the context in which products and services are introduced from the view point of the novelty of the product and/or market." Position innovations can be both driven by product innovation and process innovation. I consider position innovation in mHealth from the viewpoint of how mHealth explore new market positioning with product or service novelty for patient care. I focus on key factors that drive the growth of the mHealth-related industry and the potential innovation paths that corporate development strategies may adopt.

Paradigm innovation is defined as "changes in the underlying mental and business models that frame what the organization does" [86]. Existing literature advises that paradigm innovation can be triggered by many different sources, from new technologies, the emergence of new markets with different value expectations, new legal rules of the game, to changes in environmental conditions. Applying paradigm innovation in mHealth can mean affecting the existing business model of medical systems by introducing mHealth. For this thesis, I defined paradigm innovation as "changes in the underlying mental and business models which frame what the medical system adopts." I consider paradigm innovation in mHealth from the viewpoint of the relationship between regulation and mHealth innovation as being behind mental and business model changes. Along with the emergence of innovation in the regulated industry of medical care, the emergence of mHealth will be examined from various perspectives to identify what makes it different from drug and medical device innovations.

Table 1-1. Definition of 4Ps of innovation

Type of innovation	Original definition [86]	Definition in this thesis
Product innovation	Changes in the things (products and services) which an organization offers.	Changes in the products and/or services with respect to technological novelty or fusion.
Process innovation	Changes in the ways in which they are created and delivered.	Changes in the ways that clinical trials and medical delivery processes, specifically are created and delivered.
Position innovation	Changes in the context in which the products and services are introduced.	Changes in the context in which products and services are introduced from the viewpoint of the novelty of the product and/or market.
Paradigm innovation	Changes in the underlying mental and business models which frame what the organization does.	Changes in the underlying mental and business models that frame what the medical system adopts.

Drastic changes in the existing medical system and business models by introducing mHealth

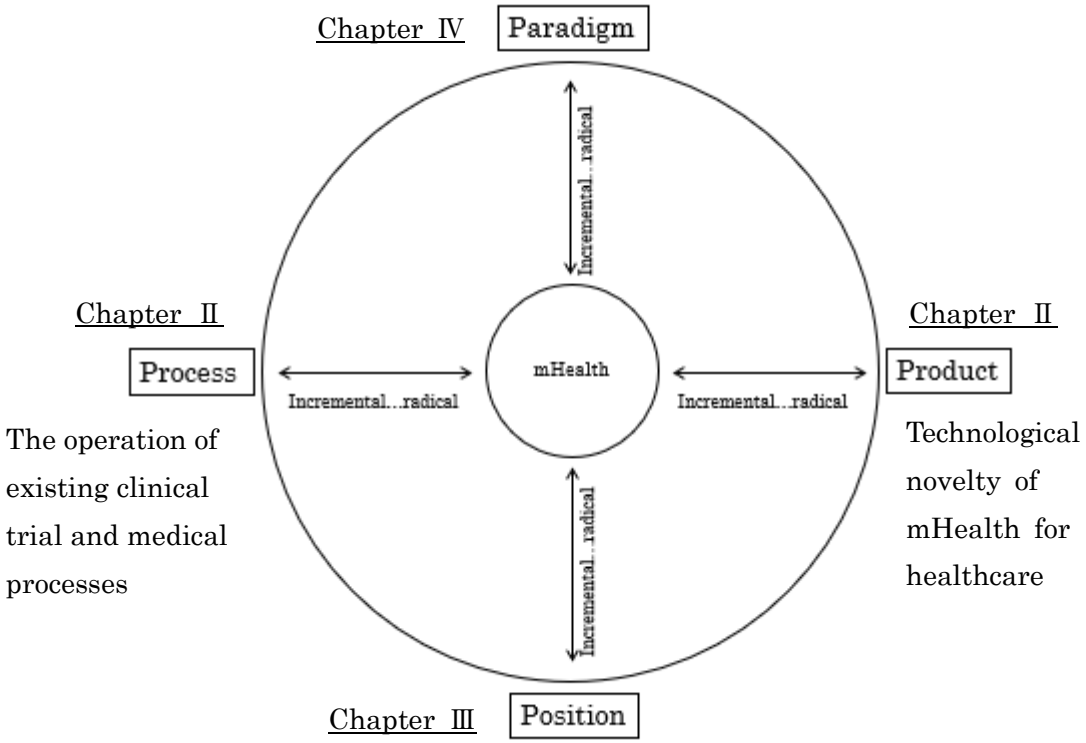

Figure 1-1. Framework for the whole thesis

1.6. Chapter structure of this thesis

The conceptualization of the theoretical framework has four different research phases; each research phase has a different research aim. The first phase and starting point of the research, chapter 1, is to review the current status and literature of mHealth to decide the scope and objective of this thesis.

The aim of phase two of the research is to examine mHealth from the perspective of technology and innovation management based on the current status of clinical trials related to mHealth. In this phase, chapter 2, I focus on product and process innovation of mHealth. In order to observe the mode of innovation, I carefully considered the theory on product and process innovation [93]. Essentially, although product innovation is still in the introduction phase, process innovation is simultaneously ongoing as improvements in production costs in the diffusion phase are expected. What about the case of mHealth? One possibility is that mHealth can, in itself, become a form of product innovation in the medical field. Another innovation route for mHealth is in the form of process innovation. This comprises of improvements in existing therapies, as well as the efficiency and effectiveness of pharmaceutical clinical trials. I analyzed the technological novelty and the purpose mHealth in healthcare from the perspective of product and process innovation.

The aim of phase three of the research is to explore the key factors that drive the growth of the mHealth industry and the potential innovation pathways that need to be incorporated into corporate development strategies for possible-market positioning. In this phase, chapter 3, I focus on position innovation of mHealth. As I defined in the framework, I categorized mHealth's position into product and market novelty, and analyzed FDA-approved mHealth products and development companies. I classified FDA-approved mHealth segments into each quadrant of the Ansoff matrix [94], which is a two-by-two depiction of the options open to organizations to develop strategic options for businesses. The matrix defines four types of novelties: market penetration, product development, market development, and diversification. This matrix is useful because it provides a simple framework that encapsulates all the strategic directions an organization can adopt through a single analytical tool. The products were grouped into these quadrants in terms of the novelty of the market in which a product is developed and the novelty of the product itself, to analyze product positioning for mHealth.

The aim of phase four is to examine the impact of mHealth on medical systems and identify the paradigm innovator in mHealth. In this phase, chapter 4, I focus on paradigm innovation of mHealth. Based on the survey on mHealth in the United States conducted in research phases 1 and 2, I focused on the interaction

between regulation and innovation compared to the existing pharmaceutical and medical device industries. Regulations have two sides: one that prevents serious adverse effects to the rights, safety, and lives of citizens, and the other that restricts innovation and causes a chilling effect, as well as opportunity loss. It is expressed as “innovation-first/regulation-after” [77]. The maintenance of an appropriate balance between innovation and regulation, and the methods of realizing the purpose of regulations change with the progression of the technology of the particular time and society. Thus, it is necessary to discuss regulations that reflect the changes in the structure of society and industry. The relationship between regulations and industry was investigated through interviews, and paradigm innovation in mHealth was considered based on the facts of this relationship; a proposal was then explored.

The aim of phase five is to state the main findings of this thesis. In this phase, chapter 5, I argued that both the academic and practical contributions of my thesis are based on the analysis of the 4Ps of innovation in mHealth. I clarify the starting place in mHealth innovation and identify areas in need of an innovative approach.

Table 1-2. Structure, research questions, and methods used for this thesis

Chapter	Title	Target innovation of 4Ps	Research question	Method
1	Introduction	-	What is the current state of m Health research?	Empirical Study
2	Exploring the potential of mHealth in product and process innovation	Product and Process innovation	1. What kind of technologies are applied to mHealth products and services with respect to technological novelty or fusion? 2. How mHealth improve the operation of existing clinical trial and medical process with product and services?	Empirical Study
3	Positional innovation of mH ealth: An overview of FDA-approved mobile medical ap plications	Position	1. What kind of technologies a nd services are being introd uced? 2. What are the key factors dr iving the growth of the mH ealth industry and potential innovation pathways for po ssible-market positioning?	Empirical Study
4	The impact of mHealth on medical systems	Paradigm	What is an innovator in mHealt h to improve in healthcare comp ared to pharmaceuticals and me dical devices?	Semi-structured interview
5	Conclusion	All	Academic and practical contribut ions based on the 4Ps analysis by delving into the background and implications of the advent o f mHealth in healthcare industr y.	-

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CHAPTER 2. EXPLORING THE POTENTIAL OF MHEATLTH AS PRODUCT AND PROCESS INNOVATION FOR HEALTHCARE

2.1. Introduction

Mobile Health or mHealth is an emerging concept of the use of mobile devices and wireless technology for healthcare purposes. Recently, mHealth-related technology is expected to form a new category of medical devices particularly in the monitoring of patients. This is also anticipated to improve the efficiency and effectiveness of pharmaceutical clinical trials. However, there are challenges to utilize this enabling technology to innovate the pharmaceutical and medical devices business.

The main objective of this chapter is to explore the potential of mHealth from the perspective of product and process innovation based on the below-mentioned hypotheses. First, I position mHealth with respect to current innovation theories based on intensive literature review. Second, I hypothesize that mHealth has two potential areas of innovation: product innovation in the medical devices industry and process innovation in the pharmaceutical industry. To test the hypotheses, I conducted a holistic observation on clinical trials to examine how large mHealth impacts a treatment pathway by innovative products. In the observation, I determined the current status of clinical trials with mHealth registered in ClinicalTrials.gov and analyzed the trend of mHealth related technology in clinical trials. As a result, I confirmed a diverse deployment of mHealth-based approaches across therapeutic area and disease. The present study forms the basis of technological forecasting for mHealth based innovation.

2.2. Related studies

In consideration of the standpoint of mHealth technology management, I postulated representative theories on technology and innovation management [1] [2] [3] [4] [5].

First, I considered the phase of innovation through reference to Rothwell's classification of technological transitions [4]. According to this classification, a linear model of technology push and demand pull prevailed in the first and second generations, a coupling model of R&D and marketing arose in the third generation, a parallel model or the Kline model represented the fourth generation, and a networking model arose in the fifth generation.

In order to observe the mode of innovation, I carefully considered Abernathy and Utterback's theory on product versus process innovation [1]. Process innovation

refers to improvement in the production processes and production technology of existing products, and through new processes of production, reducing product costs, or improving quality and performance through technological innovation. Product innovation corresponds to technological innovation; it is presumed that technological innovation has the potential to produce revolutionary new products that did not previously exist [5].

Thirdly, I investigated the innovation process stage, according to Rogers' and Moore's theories [3] [4]. When recording the state of diffusion on a time axis, along with the number of adopters, with regularity, the normal distribution of adopters shows a bell-shaped curve [3]. The numbers relating to each adopter classification, which can be roughly determined from trends in either the number of people reached or the market share, show an S-shaped curve [3]. Moore argues that, with regard to the behavior of users in high-tech marketing, there are cracks between individual types of adopters in particular, and there is a chasm between early adopters and early majority [4].

Finally, I tested the applicability of the theory of disruptive innovation information [6]. Information and communication technology (ICT) is said to play two important roles in promoting a disruptive business model in healthcare. First, it reportedly promotes cooperation between doctors, nurses, and patients during medical treatment, and transitions healthcare towards being a network-style business. Second, by promoting cooperation between healthcare providers and digitizing medical information such as patient records, the efficiency of clerical work can be greatly improved. I believe that, with its expected growth, mHealth will help improve productivity in the development of pharmaceuticals. Through consideration of mHealth from the standpoint of technology management, in line with existing innovation research, we have developed three hypotheses, as described below.

2.2.1. Current understanding and hypothesis

For my first point, I will focus on the dissemination process of innovations. mHealth is in the introduction phase of the current medical market. Rogers reports the percentages of adopters during the diffusion of new technologies and services, in relation to the total market, to be at 2.5% for innovators; 13.5%, for early adopters; 34%, for early majority; 34% for late majority; and 16% for laggards [3]. According to this standard, healthcare businesses that use mobile phone and smartphone apps are currently considered to be early majority.

Meanwhile, mHealth has been progressing rapidly in terms of uptake and diffusion in the medical field. The global medical market size is said to be around

9.59 trillion USD [7]; within that, the market size for mHealth is 10.5 billion USD (0.11%) [6]. However, according to a survey, the number of people who use mobile phone and smartphone apps for self-tracking was approximately 7% in 2010 [8], and according to a 2012 survey, that percentage subsequently increased to 19% [9]. Additionally, with the spread of smartphones and wearable devices, a daily increase has been observed in healthcare-related IT products [10].

The implementation of mHealth is also progressing in clinical research and development. Clinical research related to mHealth has been on the rise since 2008 [11] [12]. In clinical research, mHealth has been used in many different sub-fields, including health promotion and disease prevention, diagnosis, treatment, monitoring, and support for health services [13] [14] [12]. Based on the above, it can be said that mHealth is becoming a part of the clinical research through the uptake and diffusion of information and communication technology. In particular, based on the benefits of being able to access data in real time, advancements in the use of mHealth for drug development are also expected.

H1: mHealth including mobile phone, smartphone, and application technologies has a potential to be adapted for the improvement of productivity in the development of pharmaceuticals.

For my second point, I will be looking at the types of innovation. In the case of product innovation in pharmaceuticals, up until the 1970s, the utilization of natural compounds and the chemical synthesis of small molecules were mainstream. Since the 1980s, however, biological medicine using gene recombination technology has been developed, and research in the treatment of diseases that are difficult to cure is still in progress [15] [16]. In addition, the new innovation involving use of cell therapy and regenerative medicine to treat tissues and organs has also emerged, in place of use of substances in this regard [17]. As for process innovation, regarding small molecules, sophisticated rapid-screening technology and formulation technology has been developed. At the same time, developments in biological medicine require even more advanced technology, and the sharp rise in R&D costs has led to problems relating to a decline in productivity in this field [18]. That is to say, in light of previous research and observations [19], while small molecule-related matters are at a stage where they are being led by process innovation, biological medicine is considered to have remained at the stage of product innovation.

In the case of medical equipment, product innovations including devices such as catheters and portable blood inspection machines that can perform various

analyses from a drop of blood [20]contribute to early detection and treatment of diseases, due to diagnostic equipment and the development of surgical instruments [21]. Process innovation involves improving equipment through miniaturization, making them lightweight and noninvasive, as well as increasing the degree of precision [6]. Additionally, in the development of products that primarily target developing countries, focus has been on features such as simplicity and low costs, and there are cases where such products even expand to developed countries, as well [22]. That is to say, while product innovation takes the lead, process innovation pioneer's new therapeutic purposes and applications, such that the two innovations work mutually.

Product innovations in the cell therapy and regenerative medicine field include wound healing through use of cultured skin, cancer immunotherapy using dendritic cells, and regenerative medicine using stem cells, which are all on the market. In particular, the use of regenerative medicine to fundamentally restore the function of damaged organs and tissue has created new treatment possibilities for diseases and disorders that were previously difficult to treat [23]. Process innovation in stem cell-related technologies, such as safe and efficient production of cells of a consistent quality, achievement of cell separation, regeneration, conservation, and so forth, has advanced [24]. Essentially, although product innovation is still in the introduction phase, process innovation is simultaneously ongoing, as improvements in production costs in the diffusion phase are expected.

What about the case of mHealth? One possibility is that mHealth can, in itself, become a form of product innovation in the medical field. For example, Otoharmonics developed the LevoSystem app for the treatment of tinnitus and obtained clearance from the Food and Drug Administration (FDA) 510(k)[25]. Doctors "prescribe" the app to patients, and through training of the brain to ignore tinnitus sounds, therapeutic effect is achieved.

Another innovation route for mHealth is improvement of existing therapies and the efficiency and effectiveness of pharmaceutical clinical trials [26]. WellDoc, Inc. developed BlueStar as a software application for guiding the treatment of Type 2 diabetes patients. BlueStar is the first application to achieve the trifecta of FDA-cleared, physician-prescribed and payer-reimbursed digital medicine product [27]. Patients download BlueStar, prescribed by their doctors to their smartphones and tablets. Patients' blood sugar levels are measured in real time; they also receive individual guidance concerning the content of their treatment and lifestyles from doctors and experts. The results of clinical trials showed improvement in hemoglobin A1c scores (HbA1c) over a 12-month period [28]. Moreover, WellDoc, Inc. has

positioned BlueStar as mobile prescription therapy (MPT) [29]. Furthermore, real-time data gathering with respect to mHealth is expected to open the door for drug developers to improve drug development in the following ways: enhancing patient safety, strengthening the quality of data, and accelerating the duration of development [30]. Indeed, several leading pharmaceutical companies are adopting this technology for smarter development of new drugs in a faster, safer, clearer, and more cost-friendly manner [31] [32] [33]. However, there are challenges to the utilization of this technology to innovate the pharmaceutical and medical devices business. Based on the considerations mentioned above, I present the following hypothesis:

H2: mHealth reaches two potential areas of innovation: 1) product innovation per se, for medical use, and 2) contribution to process innovation in pharmaceutical product development.

As a third point, I will focus on the dynamics of innovation. Mowery and Rosenberg et al. classified technology push based on an innovation pattern set to improve the performance of technology, and demand pull as technological advances made in response to the needs of specific markets [34]. Against the background of the growth of mHealth in recent years, the technical aspects of devices and within communication technology have shown substantial advancement. In the 1990s, Tarner et al. developed technology using compact and lightweight cameras and head mounted displays（HMDs [35], and because of this, a mobile, wearable method for inexpensively collecting and storing data in real time became possible [36]. Moreover, through faster communication, it is now possible to quickly and safely share medical information [37], since sending and receiving large amounts of data, especially with the development of cloud services, became possible. From this, it is inferred that technology push has become a driving force behind innovation.

Meanwhile, the adaptation of mHealth to cognitive behavioral therapy for mental disorders has displayed different appearance. In this field, mHealth is expected to promote collaboration between doctors, nurses, and patients, and networking between patients and families. There are many recent apps available that are expected to work as tools to help improve patients' conditions [38] [39]. However, in actuality, although several apps are commercially available for the treatment of and therapeutic support for mental disorders, a lack of evidence proving their effectiveness should be pointed out [40] [41]. It follows from that, there are signs of innovation resulting not only from technology push, but also as a result of

demand pull. Based on the considerations mentioned above, I present the following hypothesis:

H3: In order to implement mHealth in pharmaceutical R&D, technology push is the current driver for the innovation associated with mHealth.

2.3. Materials and Method

2.3.1. Database of holistic observation of clinical trials

In December 2015, two electronic databases of clinical trials (ClinicalTrials.gov and WHO International Clinical Trials Registration Platform) were systematically searched. In this study, I use ClinicalTrials.gov as a database, to determine the current status of clinical trials using mHealth. However, US federal law requires the registration at ClinicalTrial.gov to include information about federally or privately funded clinical trials conducted under investigational new drug applications, to test the effectiveness of experimental drugs for patients with serious or life-threatening diseases or conditions [42]. Therefore, ClinicalTrials.gov currently lists more than 200,000 studies, with sites in all 50 states and in 191 countries. Furthermore, the USA is a leader in the mHealth market [6]. ClinicalTrials.gov is a registration and results database of publicly and privately supported clinical studies conducted on human participants around the world. The website is maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH). The information on ClinicalTrials.gov is provided and updated by the sponsor or principal investigator of each clinical study. For the reasons mentioned above, I decided to use ClinicalTrials.gov to cover many clinical studies around the world.

I could find wide-ranging information on the website, as each ClinicalTrials.gov record presents summary information about study protocol, including the following: Disease or condition, intervention (e.g., the medical product, behavior, or procedure being studied), title, description, study design, requirements for participation (eligibility criteria), locations where the study is being conducted, and so on.

2.3.2. Search strategy

Number: A list of keywords was created in the two domains of “mobile health” OR “mhealth;" our target was intervention studies.

2.3.3. Classification of Conditions

I classified the conditions of the mHealth clinical trials according to 23 categories of the International Classification of Diseases (ICD)-10 version 2015 [43]. The ICD is the standard diagnostic tool for epidemiology, health management, and clinical purposes. The ICD is used by physicians, nurses, other providers, researchers, health information managers and coders, health information technology workers, policymakers, insurers, and patient organizations, to classify diseases and other health problems recorded on many types of health and vital records, including death certificates and health records. The ICD-10 was endorsed by the Forty-Third World Health Assembly in May 1990 and came into use in WHO's member states, as from 1994 [43]. I decided to use the ICD-10 to understand the major categories of mHealth clinical trials.

2.4. Results

2.4.1. Holistic observation of clinical trials

A search identified 199 studies with the two domains of [“mobile health” OR “mhealth"], on December 23, 2015. Of the 199 studies, 193 intervention studies were identified (6 intervention studies were blank). Clinical studies using mHealth are conducted all over the world. However, more than half are conducted in the US. I found that the registered status of 22 of the studies in the database was Phase 1. The phase numbers for the different studies were as follows: Phase 0 in two studies, Phase 1 in five studies, Phase 1/2 in three studies, Phase 2 in four studies, Phase 2/3 in one study, Phase 3 in four studies, and Phase 4 in three studies. For three of the studies, the results status was “Has results,” but no statistical analysis was provided, to enable evaluation of the intervention impact of mHealth for each study. The results status of the other studies was “no results available.”

2.4.2. The potentiality of mHealth for pharmaceutical product development

As for the starting date of clinical trials using mHealth, the number is increasing after 2012 (Figure 2-1). According to "Trends, Charts, and Maps" of clinical.gov, there were 23,297 studies clinical studies registered between 2014 and 2015. To determine types of interventions in the registered data, I searched for major intervention keywords. I found the major keywords to be "application," followed by "text messaging," and "smartphone" (Table 2-1). In support of Hypothesis 1, the results showed that mobile phones, smartphones, and applications have already been used for clinical trials and that there is potential for the application of mHealth in pharmaceutical development.

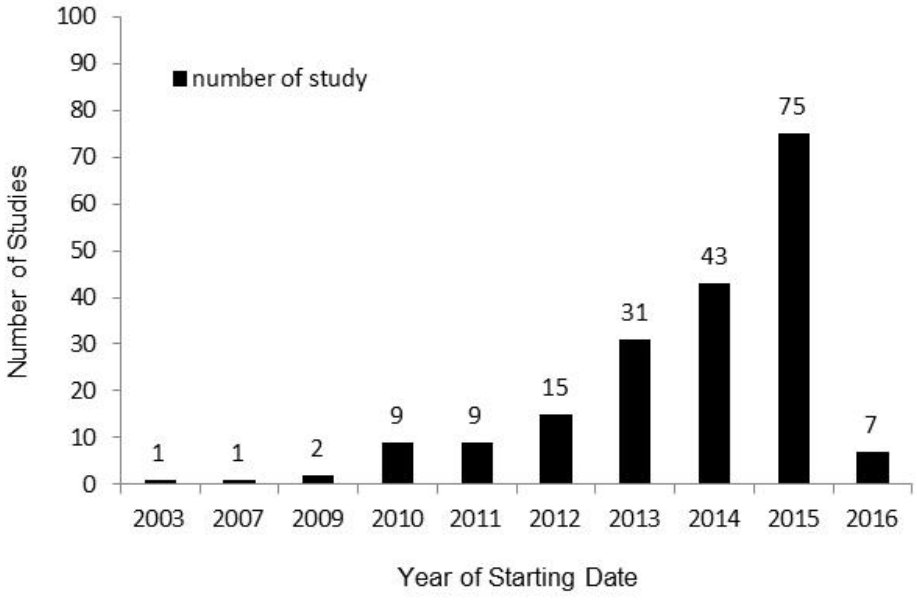

Figure 2-1. Starting date of clinical trials with mHealth

Table 2-1. Major keyword of the category of intervention

Major key word of intervention	Number
application	34
text messaging	29
smartphone	18
SMS	18
fitbit	6
facebook	2

2.4.3. The mode of innovation with mHealth

I classified 178 of 193 studies according to conditions. Fifteen of the studies were not classified using the ICD-10 because the data were not related to conditions (i.e., attendance, sedentary lifestyle). Multiple conditions were registered for some of the trials; in such instances, I used double counting. Our results showed that mental and behavioral disorders (24.2%) were the most common condition, followed by diseases of the circulatory system (19.9%), endocrine, nutritional, and metabolic diseases (18.0%), certain infectious and parasitic diseases (11.8%), and pregnancy, childbirth, and puerperium (7.0%) (Table 2). Furthermore, I noted the disease types recorded in more than 10 studies. Diabetes mellitus was the most common disease (27 studies), followed by HIV (20 studies), hypertension (10 studies), cancer (10 studies), and obesity (10 studies).

The primary purposes of 178 of 193 studies were registered on the database. Our results showed treatment (30.9%) to be the most common purpose, followed by prevention (25.8%), health service research (20.8%), supportive care (17.4%), basic science (2.2%), screening (1.7%), and diagnosis (1.1%) (Table 2-3).

Furthermore, I determined the breakdown of treatment studies. The most common purpose of treatment was medical adherence (45.5%) (Table 2-4). For medical adherence, reminders and a real-time feedback function with text messaging, as well as apps, were used to improve medical adherence. mHealth was related to other behavioral interventions.

Table 2-2. Conditions of clinical trials with mHealth

Category of ICD-10 version 2015	Number	%
V Mental and behavioural disorders	48	(24.2)
IX Diseases of the circulatory system	37	(19.9)
IV Endocrine, nutritional and metabolic diseases	34	(18.3)
I Certain infectious and parasitic diseases	22	(11.8)
XV Pregnancy, childbirth and the puerperium	13	(7.0)
II Neoplasms	10	(5.4)
X Diseases of the respiratory system	9	(4.8)
XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	3	(1.6)
XIII Diseases of the musculoskeletal system and connective tissue	4	(2.2)
XIX Injury, poisoning and certain other consequences of external causes	4	(2.2)
VI Diseases of the nervous system	2	(1.1)
XXI Factors influencing health status and contact with health services	0	(0)
XVI Certain conditions originating in the perinatal period	0	(0)
III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	0	(0)
VII Diseases of the eye and adnexa	0	(0)
VIII Diseases of the ear and mastoid process	0	(0)
XI Diseases of the digestive system	0	(0)
XII Diseases of the skin and subcutaneous tissue	0	(0)
XIV Diseases of the genitourinary system	0	(0)
XVII Congenital malformations, deformations and chromosomal abnormalities	0	(0)
XX External causes of morbidity and mortality	0	(0)
XXII Codes for special purposes	0	(0)

Note: the number of categories was double-counted since there were several trials registered in multiple conditions.

Table 2-3. Primary purpose and intervention

Primary purpose	Number	%
Treatment	55	(30.9)
Prevention	46	(25.8)
Health Services Research	37	(20.8)
Supportive Care	31	(17.4)
Basic Science	4	(2.2)
Screening	3	(1.7)
Diagnosis	2	(1.1)

Table 2-4. The items of treatment

The items of Treatment	Number	%
Medication adherence	25	(45.4%)
Other Behavioural Intervention	21	(38.1%)
Monitoring	7	(12.7)
Improving workflow between physicians and other health care professionals	1	(1.8)
Education for health workers	1	(1.8)

To clarify how mHealth intervened in studies, I extracted the breakdowns of other behavioral interventions. I classified therapy or therapy support based on the primary endpoint of each study, regardless of whether it was combined with standard therapy. Our results showed that in 12 of 21 other behavioral intervention studies, interventions were examined as therapy and in 9 interventions were examined as supplementary to therapy (Table 2-5). With regard to use of the intervention as therapy, I found potential for mHealth to be used as therapy for alcohol abuse, as cognitive behavioral therapy for depression, and for smoking cessation and drug dependence, without use of medicine. mHealth is used to determine appropriate treatment for patients with mental conditions and addictions through use of mobile devices, in particular, text messaging and push notifications through apps. As a supplement to therapy, the inter-operability and remote function of mHealth are used to support existing therapy treatments; for example, the provision of rehabilitation program via mHealth, to implement a lifestyle intervention. Therefore, it becomes clear that mHealth has the potential for product innovation as a form of therapy, and also for process innovation as a means of support for existing therapy

treatments. However, such potential has yet to be realized in pharmaceutical R&D. Currently, improvement of medical adherence predominates in clinical trials adopting mHealth. Overall, these observations are partially supportive of Hypothesis 2.

Table2-5. The items of other behavioral interventions

The items of other behavioral interventions		Number
Therapy		12
	Alcohol abuse treatment	(3)
	Smoking cessation treatment	(3)
	Cognitive behavioral therapy (CBT) for depression, Schizophrenia	(2)
	Drug Dependence	(2)
	Adolescent Obesity treatment	(1)
	Traumatic Brain Injury care system	(1)
Therapy support		9
	Rehabilitation support	(3)
	Lifestyle interventions	(3)
	Self-management plus standard care	(2)
	Pain Coping Skills Training	(1)

2.4.4. The dynamics of innovation with mHealth

I found that many devices are used in a wide range of interventions not limited to medical devices only, but also applied to commercial uses for healthcare. In the registered data, I extracted the primary purposes and interventions relating to the most common conditions (mental and behavioral disorders, diseases of the circulatory system, and endocrine, nutritional, and metabolic diseases) as classified by the ICD-10 to identify intervention uses of mHealth. These results show that most mHealth interventions are based on simple device functions, such as text-messaging and apps, to improve adherence (Table 2-6). From this result, I concluded that current efforts relating to innovation using mHealth are not technology driven, which proves incompatible with Hypothesis 3.

I also examined the founders and sponsors/collaborators of the clinical trials that I observed. Approximately 75% of studies were funded by others, followed by the NIH (12%), “other” (13%), industry (9.2%), and U.S. Federal Agency (U.S. Fed.) (Table 2-7). Of the clinical trials using mHealth, 51% were sponsored by universities and colleges, 18% by institutes, and 15% by hospital and medical centers. No major pharmaceutical company was indicated as a sponsor/collaborator in the registered data. It is inferred that, with the growth of the mobile phone and smartphone, and the enforcement of the Mobile Medical Applications Guidance for Industry and Food

and Drug Administration Staff in 2013 [44]. mHealth not only has potential for use in health tracking, but also offers a challenge to university and college centers regarding the use of mobile technologies to improve health outcomes. I identified few biopharmaceutical or other firms as sponsors in more than two clinical trials; these were RAND, Verizon Wireless, Proteus, Coherohealth, and Dimagi Inc. I also identified industries using mHealth in clinical trials (Table 2-8).

Based on the results, I determined the type of study conducted by each industry and the type of technology developed. RAND, Verizon Wireless, Proteus, Coherohealth, and Dimagi Inc. conducted clinical trials to improve medication adherence. For example, Verizon, being the largest wireless telecommunications provider, determined the impact of an integrated mobile health system, Verizon Wireless's Converged Health Management (CHM), on heart failure and related quality of life [45]. Verizon Wireless's CHM, a remote patient-monitoring medical platform, is designed to help clinicians and patients manage patient health in-between doctors' visits; in 2014, the system received clearance from the U.S. FDA 510(k) to run on the iOS (Apple, Inc.) mobile operating system [46]. Dimagi Inc. is a recognized social enterprise and certified benefit corporation committed to building mobile systems for local environments [47].

The enterprise conducted a clinical trial to evaluate a cellular phone-based system that assists patients with medication adherence. There is an intervention involving use of text-messaging or an interactive voice response (IVR), and an electronic pill container device. If the patient does not open the pill container, the system recognizes this as a failed dose and the intervention subject receives personalized reminder messages on his/her mobile phone. These results indicate industry-driven development of mHealth, with the use of devices, apps, and platforms. However, the current industry players remain at the stage of using only available technology to improve medication adherence, within the boundaries of clinical developments wherein telecom providers have diversified into healthcare.

Table 2-6. Primary purpose and intervention: Mental and behavioral disorders, Diseases of the circulatory, endocrinal, nutritional and metabolic diseases

Category of ICD-10 version 2015	Primary purpose	Number	Intervention
V Mental and behavioral disorders	Treatment	17	application (6) text message(2) application and sensor (1) WatchPAT sleep monitor and CBT-i Coach mobile app (1) mobile phone(1) mobile phone(game)(1) therapeutic interactive voice response (1) application and Interactive Voice Response (1) website and SMS (1) Facebook and messaging (1) mobile health care system (1)
	Prevention	8	text message (5) application (3)
	Health Services Research	4	application (1) Ingestion Sensor and Wearable Sensor (1) mHealth (1) tablet (1)
	Supportive Care	2	text message (1) applications and web-based links (1)
	Basic Science	1	Misfit (1)
IX Diseases of the circulatory	Prevention	10	application (2) application and SMS(3) textmessage (2) iRhythm ZIO XT Patch and Wristband by Amiigo (1) SEEQ, Cardiocom and DocView(1) Fitbit Physical Activity Monitor, iHealth Glucometer, Withings Blood Pressure and application (1)
	Treatment	9	application (4) text message(3) bundled wireless real time medication reminder system and blood pressure monitoring system (1) wireless sensor monitoring and feedback (1)
	Supportive Care	5	text message (3) mobile monitoring system (1) phone call (1)
	Health Services Research	4	feedback via phone or email (1) application (1) mobiletechnology (1) textmessage and monitoring (1)
	Basic Science	1	iHealth BP7-Wireless Blood Pressure Wrist Monitor (1)
	Diagnosis	1	proteus(1)
	Screening	1	Converged Health Management (1)
IV Endocrine, nutritional and metabolic diseases	Treatment	10	application(6) application and feedback(1) application and fitbit(1) application, textmessageig and fitbit (1) textmessage, facebook and Physical Activity Monitor(1)
	Prevention	8	application (1) text message (1) SMS(1) application and SMS (1) monitoring (1) text message and social media(1) fitbit Ultra, Pedometer and application(1) website (1)
	Health Services Research	9	application (4) text message (2) on line self report (1) Mobile Health Care System (1) electronically-mediated CardioMetabolic Program (1)
	Supportive Care	6	application (4) text message (2)
	Basic Science	1	iHealth wireless scale, application and text message (1)

Table 2-7. Founder of clinical trials with mHealth

Founder	Number	%
Other	187	(75.1)
NIH	30	(12.0)
Industry	23	(9.2)
U.S. Fed	9	(3.6)

Table 2-8. Sponsor/Collaborators of clinical trials with mHealth

Sponsor/Collaborators	Number
University of California, San Francisco	14
Boston University	8
Duke University	8
University of Washington	7
Massachusetts General Hospital	6
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	6
National Institute of Mental Health (NIMH)	6
University of California, Los Angeles	6
Dartmouth-Hitchcock Medical Center	5
Johns Hopkins University	5
National Institutes of Health (NIH)	5
The Miriam Hospital	5
University of British Columbia	5
Icahn School of Medicine at Mount Sinai	4
London School of Hygiene and Tropical Medicine	4
National Institute on Drug Abuse (NIDA)	4
University of Nairobi	4
University of Pittsburgh	4
University of Southern California	4
VA Office of Research and Development	4
Yale University	4
Boston Medical Center	3
Children's Research Institute	3
CoheroHealth	3
Dimagi Inc.	3
George Washington University	3
Mayo Clinic	3
McKesson Foundation	3
Medical University of South Carolina	3
National Heart, Lung, and Blood Institute (NHLBI)	3
Patient-Centered Outcomes Research Institute	3
RAND	3
Rhode Island Hospital	3
University of Michigan	3
American Heart Associatio	2
Cedars-Sinai Medical Center	2
Columbia University	2
Department of Health and Human Services	2
Eunice Kennedy Shriver National Institute of Child Health and Human Developme	2
Institute for Clinical Effectiveness and Health Policy	2
Johns Hopkins Bloomberg School of Public Health	2
Johns Hopkins Bloomberg School of Public Health	2
Kenyatta National Hospital	2
Marie Stopes International	2
McMaster University	2
Medical College of Wisconsin	2
National Cancer Institute (NCI)	2
National Cancer Institute (NCI)	2
National Institute of Nursing Research (NINR)	2
New York University	2
Northwestern University	2
Proteus Digital Health, Inc.	2
Seattle Children's Hospital	2
Universidade Lusófona de Humanidades e Tecnologias	2
University of California, Davis	2
University of California, San Diego	2
University of California, San Diego	2
University of Cape Town	2
University of Copenhagen	2
University of Florida	2
University of Malaga	2
University of Miami	2
University of Oxford	2
University of Pennsylvania	2
Vanderbilt University	2
Verizon Wireless	2
Wellcome Trust	2
Scripps Translational Science Institute	2

Note: the number of founders was double-counting since there were several trials registered in multiple founders.

2.5. Discussion

2.5.1. The potentiality of mHealth for pharmaceutical product development

In the innovation process related to pharmaceutical development, I consider the positioning of mHealth (Hypothesis 1). Clinical trial data show that the number of studies conducted has increased since 2013. This overlaps with the spread of mobile phones and smartphones. Additionally, the FDA issued the "Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff," the guidelines of which have proved relevant for mHealth. Mental and behavioral disorders such as bipolar disorder accounted for 24.2% of disease classifications in the clinical trials, with cardiovascular disorders such as high blood pressure and heart failure followed by endocrine metabolic disorders such as diabetes. Based on these results and the "chronic quadrangle: behavior-intensive diseases with deferred consequences" shown in previous studies [6], schizophrenia, bipolar disorder, Type 2 diabetes, and so forth, are applicable. Each of these disorders requires a high degree of behavioral change, and it is difficult to determine the effects of their respective treatments; this points to a movement towards the use of mHealth. Additionally, it is suggested that ophthalmology and skin conditions, among others, are not suitable targets for mHealth, as they are proactively treatable and can be resolved through various other techniques.

Typically, there are some industries other than the medical and pharmaceutical fields as sponsors of clinical trials using mHealth. As sponsors, think tanks, telecommunications companies, and other companies developing sensor technology are building short message service (SMS) and feedback systems that use sensor technology, and conduct clinical trials aimed at improving patients' adherence. When the aim is improvement of adherence, the technological target becomes an application for communication between healthcare workers and patients, rather than providing of specialized medical knowledge. These technologies need not take a long time to measure effectiveness. Therefore, different industries may enter the field.

2.5.2. The mode of innovation with mHealth

Next, I consider the position of mHealth regarding innovations in pharmaceutical developments (Hypothesis 2). When examining the application-specific breakdown for the observed clinical trials, mHealth was introduced into trials to improve adherence; this aim accounted for 45% of the total. In the treatment of chronic diseases, the proportion of patient adherence does not exceed 50–60% [42], and due to insufficient adherence, there is an estimated 100 billion USD in hospital

expenses annually [48]. Although there is an urgent need for improvement in adherence, from the standpoint of the medical economy, the establishment of a care system that takes care of individuals is challenging. However, current hospital profit models are optimized to manage peak symptoms and acute phases. Under these circumstances, mHealth is considered to meet the needs of lower healthcare costs and duration of guidance in the provision of proper treatment to patients. In particular, as a complementary treatment tool for these diseases, mHealth is setting the standard for product innovation.

Meanwhile, with regard to the concerns of this study, the feasibility of mHealth to support process innovation in the development of pharmaceuticals could not be confirmed. However, pharmaceutical companies also sense the allure of taking advantage of possibly cheap and large-scale data collection. Based on the concept of "beyond the pill" [49], pharmaceutical companies are trying to fuse drug development and digital technology, and considering building a business model of digital medicine [50] [27]. On this basis, in innovative drug development, the fusion of IT and devices is considered the way to a prosperous future.

2.5.3. The dynamics of innovation with mHealth

Finally, let us consider the position of mHealth, with regard to the innovation dynamics of pharmaceutical development (Hypothesis 3). The results of this study showed that mHealth has been studied in relation to improvement in adherence through, for example, reminding individual patients when to take their medication, so as to encourage behavioral change in this regard. The intervention methods use the functionality of mobile phones and smartphones such as SMS, or alternatively, social media such as Facebook. Across the board, improvements are not based on the advanced level of the technology in sensors and devices, but the convenience of always being able to easily make contact. As a result of that, mHealth can be expected to fill the gap with regard to aspects that are outside the reach of medical institutions, such as maintaining patients' motivation levels regarding treatment and improving communication between patients and healthcare workers [51]. However, current trends cannot deny the innovation resulting from technology push in future. In the USA in 2015, the top category for digital health funding was healthcare consumer engagement (613 million USD), followed by wearable bio-sensing devices (489 million USD), and personal health tools and health-tracking tools (407 million USD) [52]. These results suggest that there is an increase in the attention paid to the field of sensing and tracking. It is assumed that, in future, data analyses and internet of things (IoT), which represent trends in the ICT sector, will

continue reflecting the spread of mHealth.

2.6. Limitations and future perspectives

A few aspects of the limitations of our research should be considered. First, I made a particular focus on mHealth-related interventional studies to examine how mHealth affects treatment pathways. However, I made a particular focus on mHealth-related interventional studies that are usually conducted as clinical trials thus more likely registered to the ClinicalTrials.gov, rather than non-interventional studies. Second, it could not significantly impair the quality of the present study since the ClinicalTrials.gov is the largest database that registers more than 200,000 studies from 192 countries including all the studies conducted in the United States that is by far the leading country of mHealth, it is required for further improvement to take notice of other data sources. Third, the current keyword settings ('mobile health' or 'mhealth') excluded searching the records that are using mHealth but not using these wordings in the study description. Forth, there was no uniformity with regard to the trials' characteristics on the database. The extent of the information registered on the database depends on the sponsors. Therefore, I am aware of the lack of uniformity in, for example, the words and terms used. This report provides only the registration status of clinical trials using mHealth because outcomes were registered for only three studies on the database. To evaluate the outcomes of mHealth interventions, I will try to analyze the results of the clinical trials.

2.7. Conclusion

In this present study, I observed the current status of clinical trials related to mobile health or mHealth; I also characterized the related innovations from the viewpoints of stage, mode, and dynamics. First, I confirmed that mHealth has shown double-digit growth in the number of clinical trials for a wide range of indications, including mental and behavioral disorders, and circulatory, endocrinal, nutritional, and metabolic diseases, in order to improve drug adherence. Second, through in-depth analysis of these clinical trials, it was shown that mHealth has two potential areas of application: product innovation in pharmaceutical R&D, as a form of therapy in itself, and process innovation, as a supportive tool for existing therapies. With regard to product innovation, therapies using mHealth are oriented towards cognitive behavioral therapy for mental conditions and addictions, implying that mHealth are expected to enhance patient engagement. With regard to process innovation, mHealth contributes towards improved medical adherence in a considerable number of clinical trials, whereas a dominant design has yet to appear.

Third and last, I observed that the current usage of mHealth in pharmaceutical clinical trials remains at a preliminary level of technology, such as bidirectional communication using text messaging or applications. This suggests a need for further technological developments and implementation around mHealth in future. The present study forms the basis of the trend of clinical trials using mHealth and a future outlook from the viewpoint of technology and innovation management.

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CHAPTER 3. INNOVATION PROCESS OF MHEALTH: AN OVERVIEW OF FDA-APPROVED MOBILE MEDICAL APPLICATIONS

3.1. Introduction

In chapter 3, I focus on position innovation of mHealth. I defined the position innovation as "changes in the context in which the products and services are introduced from the view point of the novelty of product and/or market." The aim of the research phase three is to explore technologies and services are introducing into a market, and the key factors that drive the growth of the mHealth industry and potential innovation pathways that need to be incorporated into corporate development strategies of organizations for possible-market position. I divided the position into product novelty and market novelty, analyzed mHealth products approved by FDA and development companies. I analyzed approval status of mHealth on the medical front for 189 FDA-approved mHealth products as of 2016 and aim to pinpoint important factors for creating a market for mHealth based on positional innovation of the 4Ps of innovation space.

Mobile health or mHealth is an emerging concept referring to the use of mobile devices and wireless technology for healthcare purposes. The term, mHealth, broadly refers to "medical and public health practice supported by mobile devices such as mobile phones, patient-monitoring devices, personal digital assistants (PDAs), and other wireless devices" [1]. The diffusion of mobile phones and smartphone technologies are expanding the possibilities of mHealth [2]. Today, mobile phones and smartphones, a device armed with computing power, mobility and downloadable apps [3], that have become an essential component of our lives. In 2016, the number of mobile phone users was estimated 4.3 billion [4], and the number of smartphone users worldwide reached 2.8 billion [5].

Furthermore, the field of mobile apps for healthcare is rapidly growing. Mobile apps are software programs that run on smartphones and other mobile communication devices [6]. They can also be accessories that attach to a smartphone or other mobile communication devices, or a combination of accessories and software. The number of apps for healthcare that are published on the two leading platforms, iOS and Android, has more than doubled in only 2.5 years, reaching 165,000 by the third quarter of 2015 [7].

Along with the spread of this mobile phone and smartphone, the US Food and Drug Administration (FDA) began regulating mobile medical apps as medical devices and the FDA issued the "Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff," the guidelines of which have proved

relevant for mHealth in 2013 [8]. FDA defined “mobile platforms” as commercial off-the-shelf (COTS) computing platforms, with or without wireless connectivity, that are handheld in nature [8]. Examples of these mobile platforms include mobile computers such as smart phones, tablet computers, or other portable computers [8]. The definition is Mobile medical application by FDA are medical devices that are mobile apps, meet the definition of a medical device and are an accessory to a regulated medical device or transform a mobile platform into a regulated medical device [8].

3.2. Related studies

Research interest in mHealth is growing, too. The majority of the published evidence in support of clinical use is limited to underpowered pilot data [4]. Some researchers have shown the current status of mHealth using systematic literature reviews [5,6], bibliometric analysis [7], and holistic observation of clinical trials of mHealth [8]. However, little is known about mHealth approved by FDA. USA is a leader in the mHealth market [9]. FDA is responsible for assuring the security and quality of pharmaceuticals and medical devices in the USA [10]. A manufacturer must obtain FDA’s prior approval or clearance before marketing many pharmaceuticals medical devices in the United States. FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States 11]. Medical devices are classified into Class I, II, and III [11]. Regulatory control increases from Class I to Class III. The device classification regulation defines the regulatory requirements for a general device type. Most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval [11]. After FDA approval, medical devices will be used for diagnosis and treatment of patients. FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States [11].

mHealth, through innovation in the field of medical innovation, has the potential to revolutionize patient care. Innovation can be classified as incremental or disruptive [11]. The theory of disruptive innovation helps explain how complicated, expensive products and services are eventually converted into simpler, affordable ones [12]. Disruptive innovation changes the market place and drives others to follow. In particular, information and communication technology (ICT) plays a role in promoting a disruptive business model in healthcare [13]. Such a technology

symbolizes markets, enterprise, and growth [14], and many firms are required to conduct activities aimed at technological innovation in a regulatory environment affected by various rules [15]. Furthermore, business strategy is the key to a firm's success and each firm is trying to position itself in the market through its distinctive corporate strategies [16].

However, in spite of its significance, few studies have addressed the dynamics of the mHealth industry from the perspective of innovation management. Previous studies provided fundamental insights into the dynamics of technological trajectories in the field of medical devices products [17-20]; the uncertainty of medical innovations and the importance of improvements through clinical practice [21][22], and a policy framework to promote medical innovation [23][24]. Nevertheless, these discussions have been to the medical devises industry i.e. not imply fusional development with other industries such as the ICT.

From the abovementioned consideration, the present study aims to understand the extent of current usage of mHealth in medical practice and to identify the key factors determining a technological pathway and driving market creation for mHealth based on positional innovation of the 4Ps of innovation space.

3.3. Materials and Methods

3.3.1. Product-based analysis

For the present study, data of mobile medical apps regulated by the FDA were retrieved from MobiHealthNews research which is an exclusive database that covers relevant FDA clearances from 1997 to 2016 [25]. It showed a total of 213 FDA clearances for mobile medical apps. Of the 213 products, I investigated products having a 510(K) number; this information can be collected from the summary of the 510(K) database of FDA [26]. These products were classified into Class I, II, or III devices. This study considers the period from 1997 to 2016 as the sample period in which FDA sends letters to the applicants. Medical devices were classified into Class I, II, and III devices [27]. Additionally, regulatory control increases from Class I to Class III devices. The device classification regulation defines regulatory requirements for a general device type. Most Class I devices are exempt from the premarket notification 510(k), most Class II devices are required to provide the premarket notification 510(k), and most Class III devices are required to get a premarket approval [27]. I found a total of 189 products that match the definition set in the present study. These products were further examined with regard to device name, 510(k) number, name of applicant, contact details of applicant, name of correspondent, contact details of correspondent,

classification product code, regulation number, date received, date on which FDA sent the letter, regulation medical specialty, 510(k) review panel, and summary in 510(K) database of FDA. The product code identifies the generic category of a device for FDA. There are 6,260 product codes in FDA, as of July 2017 [28]. Each device has a product code, and it is registered on the database. The product characteristics are classified based on the device description summary in the 510(K) database of the FDA.

3.3.2. Company-based analysis

Company-related information was retrieved from the Orbis database (Bureau van Dijk) that provides financial statement activity related information and the ownership structure for over 130 million companies across the world [29]. The selected firms that have the relevant mHealth products were classified into each quadrant of the Ansoff matrix [30], which is a two-by-two depiction of the options open to organizations. The Ansoff matrix was invented by Igor Ansoff in 1965 and is used to develop strategic options for businesses. The matrix defines four types of novelties—market penetration, product development, market development, and diversification. It is useful because it provides a simple framework that encapsulates all the strategic directions an organization can adopt through a single analytical tool [31]. The products were grouped into these quadrants in terms of the novelty of the market in which a product is developed and that of the product itself, to formulate strategies for future product and market activities. The definition of the market novelty is the presence or absence of a predicate device in FDA 510 (K) premarket notification database summary. It is classified De Novo [32]. The De Novo provides a pathway for the classification of novel medical devices for which general or special controls provide reasonable assurance of safety and efficacy for the intended use, but no legally marketed predicate device [32]. Product novelty is defined by the presence or absence of a mobile application for an existing medical device.

3.4. Results

3.4.1. The holistic view of FDA approvals to date

The number of mobile medical apps being cleared by the FDA has been increasing since 2010 (Figure 3-1). The earliest FDA clearance for a mobile medical app was in 1997 then some products were approved from 2001 to 2009. The number of clearances for mobile medical apps increased from 2010 and doubled between 2013 and 2014.

Medical specialties were registered on the 510(k) database of the FDA [27].

I classified 189 products according to regulations to clarify which therapeutic areas are being addressed with mobile medical apps. Our results in Table 1 showed that usage of medical apps for cardiovascular (49.2%) medical conditions (referred to as "medical specialty") was most common, followed by conditions whose treatment required support of (medical specialties) clinical chemistry (12.2 %), radiology (9.5%), anesthesiology (7.4%), and general hospitals (5.8%).

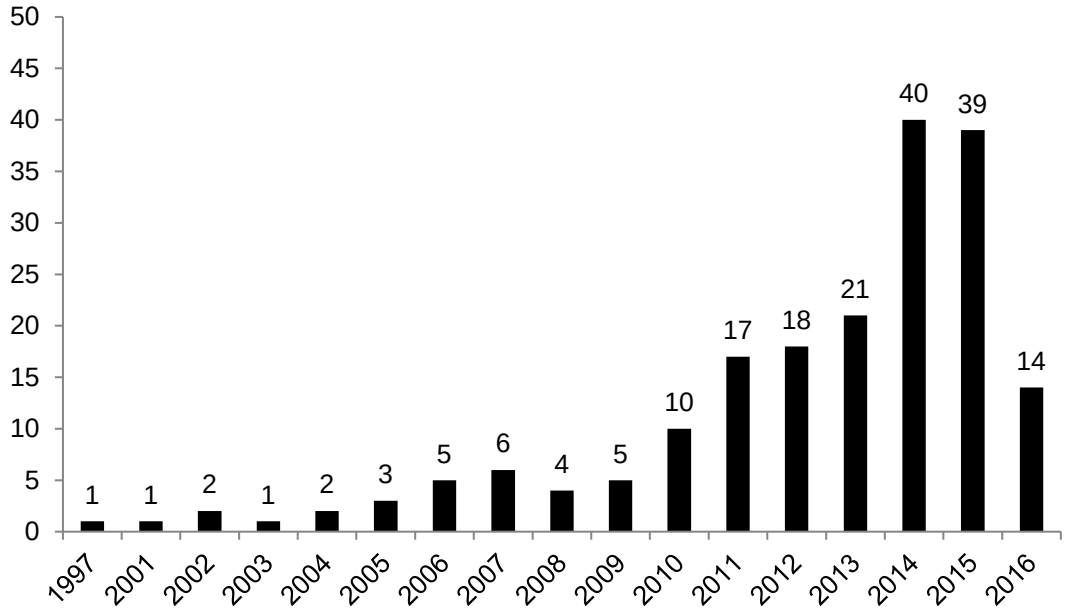

Figure 3-1. mHealth clearance by year

Vertical axis shows number of FDA clearances of mHealth, and horizontal axis shows the years of obtaining an approval.

Table 3-1. Classification of regulation medical specialty

Regulation medical specialty	Number of products	%
Cardiovascular	93	49.2
Clinical Chemistry	23	12.2
Radiology	18	9.5
Anesthesiology	14	7.4
General Hospital	11	5.8
Neurology	7	3.7
Physical Medicine	6	3.2
Obstetrics/Gynecology	5	2.6
Ophthalmic	3	1.6
Dental	2	1.1
Ear Nose & Throat	2	1.1
General & Plastic Surgery	1	0.05
Hematology	1	0.05
Microbiology	1	0.05
N/A	2	1.1

Note: the number of approved mHealth products listed in descending order of regulation medical specialty.

I also investigated regulation description (Table 3-2). Regulation description is based on product code [28]. I found that products with the following regulation description were cleared the maximum number of times: “arrhythmia detector and alarm including ST-segment measurement and alarm” (19 clearances), followed by “cardiac monitor including cardio-tachometer and rate alarm” (18 clearances), “glucose test system” (17 clearances), and “picture archiving and communications system” (12 clearances). The arrhythmia detector and alarm including ST-segment measurement and alarm and Cardiac monitor including cardio-tachometer and rate alarm was tagged under medical specialty cardiovascular, glucose test system was tagged to clinical chemistry, and picture archiving and communications system was tagged to radiology.

Medical devices are classified into Class I, II, and III based on the risk posed to patients and required level of regulatory control [10]. Of the 189 products, 181 products (96%) were Class II, 7 products were Class I, and only 1 product was categorized as Class III. FDA 510(k) cleared mobile medical apps are classified as prescription and/or over-the counter. I classified 186 of 189 products according to descriptions obtain in medical mobile apps. (3 products had no attached

information.) Of the 189 products, 132 products (70%) were classified as on-prescription, and 23% as over-the-counter.

Table 3-2. Classification of regulation description

Regulation description	Number of products
Arrhythmia detector and alarm (including ST-segment measurement and alarm).	19
Cardiac monitor (including cardiotachometer and rate alarm).	18
Glucose test system	17
Picture archiving and communications system	12
Radiofrequency physiological signal transmitter and receiver.	9
Nebulizer.	7
Noninvasive blood pressure measurement system	7
Telephone electrocardiograph transmitter and receiver	7
Noninvasive blood pressure measurement system.	5
Telephone electrocardiograph transmitter and receiver.	5

Note: the number of approved mHealth products listed in descending order of regulation description.

3.4.2. Product Characteristics and Innovativeness

In order to consider the innovation trends in mHealth in terms of typologies of the novelty, I classified these products according to the following analytical criteria of the Ansoff Matrix [30]: market penetration, product development, market development, and diversification.

The most common category was Product Development (n=171, 90% of total) whereas Diversification (n=16, 8%) and Market Development (n=2, 2%) occupied minor portions. Product development included introduction of new products in existing markets, for example, mobile patient-viewer, software-based picture archiving and communication system with mobile phone, and so on.

Miniaturization and wirelessization are the key Product development innovations. Miniaturization is achieved when products with the same function or higher performances as before are made with less volume and weight. Wirelessization reduces installation space and enhances logistics ease, thereby reducing the temporal and physical restrictions of patients during diagnosis and therapy. In our analysis, I successfully observed multiple cases in these categories, such as patient-viewer, picture archiving, and communication system. Products that

belong to Diversification can be classified into three types: (i) mHealth used in combination with pharmaceutical products to enhance their usability, e.g., Proteus's Raisin system, Welldoc Blue Star, Reciprocal Lab's Propeller System; (ii) mHealth that provide a new index of disease monitoring with novel sensory technologies, e.g., Abstats of GI-Logic; and (iii) "digital therapy" [33] for a treatment e.g. Otoharmonics' Levo System and Neurometrix's Quell.

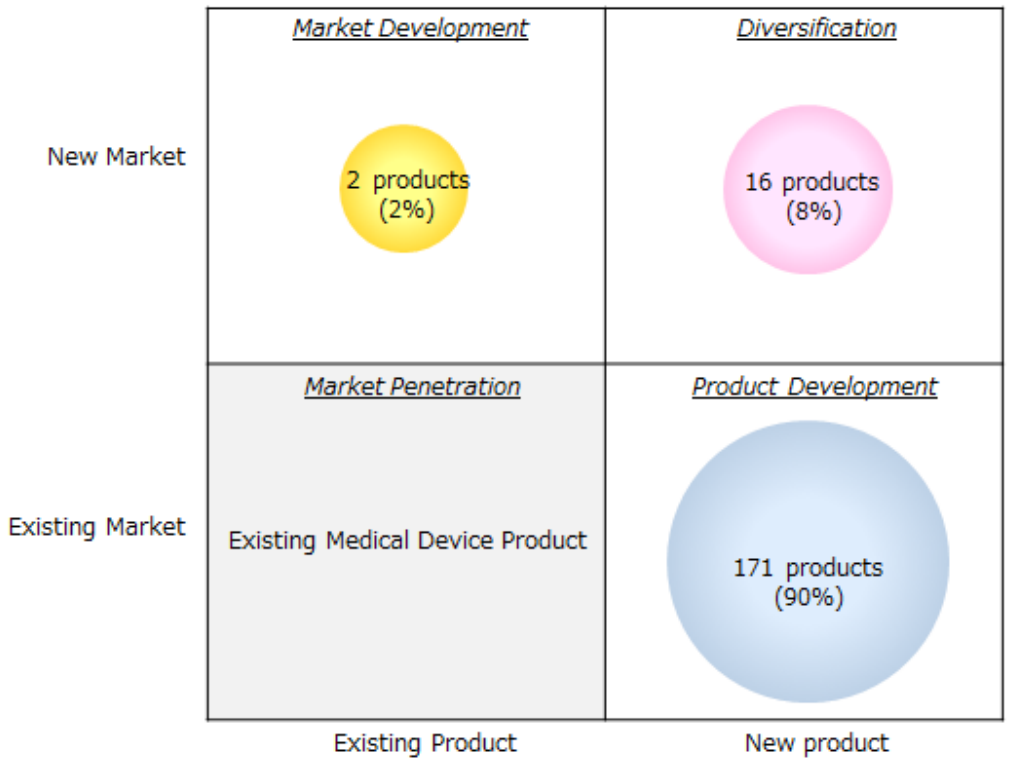

Figure 3-2. Classification of FDA-approved mHealth products on Ansoff Matrix

Products approved by the FDA were classified into each quadrant of the Ansoff matrix according to the following analytical criteria: Market Penetration, Product Development, Market Development, and Diversification.

3.4.3. Applicant Company

In order to understand the industry dynamics and corporate profiles, I examined the applicants of the approved mHealth products (Table 3-3). USA has the maximum number of applicant companies (77%), followed by China (6.3%) and Taiwan (2.1%), Australia (1.6%), Canada (1.6%), Israel (1%), New Zealand (1%), and the Netherlands (1%).

Table 3-3. Applicant Companies

Applicant company's name	Clearance product number
LifeWatch Technologies Ltd. (Card GuardScientific Survival)	11
Airstrip Technologies	10
Andon Health	9
Reciprocal Labs Corporation	7
Carestream Health, inc	5
AgaMatrix	4
Sotera Wireless	4
AliveCor, Calgary Scientific, EarlySense, Entra Health Systems, Gauss Surgical, Glooko, INTEL CORP, Proteus Digital Health, Vital Connect, WellDoc	3
ABBOTT DIABETES CARE INC, CELLCO PARTNERSHIP D/B/A VERIZON WIRELESS, DATA CRITICAL CORPORATION, GE Healthcare, Jintronix, Mega Electronics, MIM Software, Reflectance Medical, SHL TELEMEDICINE INTERNATIONAL LTD., Vital Art and Science, Welch Allyn, Withings, Zephyr Technology	2

Note: applicant company's names are listed in the descending order of product approval number.

I found significant differences between the characteristics of the companies in the new product development quadrant and the characteristics of the companies in the other two quadrants (Figure 3-2). The former group is composed of several companies that operate on a wider geographical spread, with a portfolio of multiple established products aiming at incremental innovation based on their proprietary enabling technology assets such as the telemedicine platform or wireless mobile technology. Conversely, companies under diversification have been established after 1996, are based in the United States with 18-150 employees additionally. Furthermore, founders of 4 out of 6 companies, Welldoc, Proteus, GI-Logic, Neurometrix are medical doctors (Table 3-4).

Then I investigated details of selected applicant companies that hold the largest numbers of FDA clearances in the "new product development" quadrant (Figure 3-2). The companies that have the highest number of 510(k) clearances for mobile medical apps are Card Guard (11 clearances, now a part of LifeWatch), followed by AirStrip Technologies (10 clearances), Andon Health (9 clearances), Reciprocal Labs Corporation (7 clearances), and Carestream Health Inc. (5 clearances). Details of the top three companies by clearance are described in Supplemental table 1.

The products of the following top three applicants provide convenience and functionality to patients, with miniaturization and wirelessization. LifeWatch has developed a portable electrocardiogram monitor and a portable electrocardiograph for homecare, among others. AirStrip Technologies has developed a platform that connects medical professionals with patients using mobile technology, remote patient monitor, and data viewer systems. AndonHealth has developed a smartphone-connected health device that can measure vital signs such as blood pressure, heart rate, and blood sugar levels.

Table 3-4: Company profile classified "Diversification"

Company	Year of establishment	Country	Number of Employee	Founder	Collaborator	Alliance
Neurometrix	1996	US	41	Shai N, Gozai (MD,PhD)	Harvard-MIT Division of Health Sciences and Technology	
Proteus Digital Health	2001	US	150	Andrew Thompso George Savage (MD)		2010:Novartis 2012:Otsuka Pharma
WellDoc	2005	US	88	Yves Nordmann (MD)		2014:Merck (investor) 2016:J&J (diabetes) 2018:Voluntis 2018:Samsug
Reciprocal Labs (Propeller health)	2007	US	68	David Van Sickle Greg Tracy (CTO) Mark Gehring	Robert Wood Johnson Foundation Health and Society	2015:GlaxoSmithKline 2016:Boehringer Ingelheim
Otoharmonics	2010	US	18	Michael Baker	Cedars-Sinai Medical Center	
GI Logic	2014	US	57	Brennan Spiegel (MD, MSHS), Cedars-Sinai CORE		

Table 3-5. Description of the three selected applicants in the new product development quadrant

Company		Established	Country	Regulation medical Speciality	Regulation Descreption	Device Name	Number	Year of FDA Sent Letter	Class
LifeWatch Technologies Ltd	Card Guard Scientific Survival	1986	USA	Cardiovascular	Telephone electrocardiograph transmitter and receiver	TM05 PERSONAL MEDICAL PHONE CENTER	2	2003	Ⅱ
						CG-6108 ARRHYTHMIA ECG EVENT RECORDER		2006	
					Arrhythmia detector and alarm (including ST-segment measurement and alarm).	CG-6108 CONTINUOUS ECG MONITOR AND ARRHYTHMIA DETECTOR	5	2007	
						CG-6108 ACT-3L CONTINUOUS ECG MONITOR & ARRHYTHMIA DETECTOR		2008	
						CG-6108 ACT-i L Continuous EGG Monitor and Arrhythmia Detector		2010	
						MODIFICATION TO: CG-6108 ACT-3L CONTINUOUS ECG MONITOR AND ARRHYTHMIA DETECTOR, MODEL FG-00084			
						CG-6108 ACT-3L Continuous EGG Monitor and Arrhythmia Detector		2011	
	LifeWatch Technologies Ltd		Israel	Cardiovascular	Arrhythmia detector and alarm (including ST-segment measurement and alarm).	Vital Signs Patch System (In Short Vsp)	5	2014	
						CG-6108 ACT-3L Continuous ECG Monitor and Arrhythmia Detector		2015	
						ECG Mini System Continuous ECG Monitor And Arrhythmia Detector		2016	
						Vital Signs Patch System			
AirStrip Technologies		2004	USA	Obstetrics/Gynecology	Perinatal monitoring system and accessories	AirStrip OB	3	2005	Ⅱ
						AirStrip OB		2009	
						AirStrip OB			
				Cardiovascular	Cardiac monitor (including cardiotachometer and rate alarm).	AIRSTRIP REMOTE PATIENT MONITORING (RPM) REMOTE DATA VIEWING SOFTWARE, VERSION 3.1	6	2010	
						AIRSTRIP REMOTE PATIENT MONITORING (RPM)		2011	
						Airstrip Remote Patient Monitor			
						AIRSTRIP REMOTE PATIENT MONITORING (RPM) REMOTE DATA VIEWING		2012	
						Airstrip Remote Patient Monitoring		2014	
						AIRSTRIP REMOTE PATIENT MONITORING			
				Obstetrics/Gynecology	Home uterine activity monitor	Sense4Baby	1	2015	
Andon Health Co. Ltd		1985	China	Cardiovascular	Noninvasive blood pressure measurement system.	KD-930 Fully Automatic Electronic Blood Pressure Monitor	6	2011	Ⅱ
						KD-936 Fully Automatic Wireless Blood Pressure Monitor		2012	
						KD-7964 Fully Automatic Electronic Blood Pressure Monitor			
						KD-972 blood pressure monitor		2015	
						Fully Automatic Arm Cuff Electronic Blood Pressure Dock BP3			
						Fully Automatic Electronic Blood Pressure Monitor		2016	
					Oximeter	IHEALTH FINGERTIP PULSE OXIMETER	1	2013	
				Clinical Chemistry	Glucose test system	IHEALTH ALIGN MINI GLUCO-MONITORING SYSTEM	2	2014	
						IHealth Align Gluco-Monitoring System, IHealth BG5 Wireless Smart Gluco-Monitoring System, IHealth BG5L Wireless Smart Gluco-Monitoring System		2015	

Note: three applicants in the new product development quadrant are listed in the descending order of product approval number with company's profiles and details of approved products.

I also considered the novelty of products to clarify how mHealth in medical practice is impacting the dynamics of mHealth's market. I defined novelty as "pioneering new markets" and new market as the "application market where existing equipment did not exist" compared with predicate devices. There were 18 products corresponding to new market (Figure 3-2).

Of the 18 products, 2 products were approved in Class I. These were Pixel App and Gauss Pixel App – products based on image capture technology. These apps are software programs that can be used on an iPad to capture images of sponges to assist surgical personnel in the management of surgical sponges after surgical use. Products in class II are various. Proteus has developed the Raisin Personal Monitor, a drug adherence system with ingestible sensor and a feedback and monitoring patch to monitor drug adherence for the patient [34]. Details of these companies and product profiles are described in Supplemental table 2.

Table 3-6. Description of selected three applicants for novel products

Company	Established	Country	Regulation medical Speciality	Regulation Descreption	Device Name	Number	Year of FDA sent letter	Class
Proteus Digital Health	2001	US	Cardiovascular	Telephone electrocardiograph transmitter and receiver	Raisin Personal Monitor	3	2009	Ⅱ
			General Hospital	Ingestible event marker	Proteus Patch, Proteus Ingestible Sensor		2013	Ⅱ
			General Hospital	Ingestible event marker	Proteus Digital Health Feedback Device		2015	Ⅱ
Welldoc	2005	US	-	General Hospital	DIABETESMANAGER SYSTEM, DIABETESMANAGER RX SYSTEM MODEL VERSION 1.1	3	2010	Ⅱ
			General Hospital	Infusion pump	WellDoc DiabetesManager System and DiabetesManager-Rx System		2011	Ⅱ
			General Hospital	Infusion pump	WellDoc DiabetesManager System and Diabetes Manager -Rx System		2012	Ⅱ
Reciprocal Labs corporation	2007	US	Anesthesiology	Nebulizer	Asthmapolis System	6	2012	Ⅱ
					PROPELLER SYSTEM - MODEL 2		2014	Ⅱ
					Propeller System 2014-R		2014	Ⅱ
					Propeller System		2014	Ⅱ
					Propeller Model 2014-D Sensor		2014	Ⅱ
					Propeller Sensor Model 2014-R		2015	Ⅱ
					Propeller System		2015	Ⅱ

Note: three applicants in the novel product development quadrant are listed in the descending order of product approval number with company's profiles and details of approved products.

3.5. Discussion

3.5.1. Trend of product and market development

Digital therapy for treatment has attracted the second largest investment after healthcare consumer engagement [35] [36]. The increasing amount of investment signals hopes that ICT will not only improve the medical process but also act as a means of treatment. Our findings strongly suggest that emerging mHealth products are changing the path of technological development by diversifying the information transfer process [37]. To date, information flow in medical treatment was unilateral from the doctor to the patient, and medical treatment was provided based on doctor's knowledge [38]. However, as mHealth can measure and visualize the patient's condition in real time, the patient too contributes to provide information to doctor. mHealth help patient to present objective symptom monitoring data to their doctor.

Two key factors were found to drive incremental innovation - miniaturization and the advent of wireless technology. Miniaturization of products ensures identical performance subscribing to a standard but with lesser volume, weight and functionality. Use of wireless technology can release medical practices from temporal and physical restrictions for diagnosis and therapy. Our observation supported anticipation by Christensen (2009) in which information technology can help in building a network that a doctor, a nurse, and a patient can share together [13]. Such a trend of miniaturization and adoption of the wireless technology may lead to incremental innovation in current products and services, resulting in the formation of a majority as observed in the abovementioned result (Figure 3-2).

In the field of radical innovation, small and new companies based in the United States are new market pioneers, and founders of 4 out of 6 companies, are medical doctors. Furthermore, on the contrary to incremental, significant presence of incumbent pharmaceutical and medical-product companies was observed. As seen in the case of Diversification (Figure 3-2), several mHealth products contribute to an existing pharmaceutical product to improve its adherence. In the treatment of chronic diseases, the proportion of patient adherence does not exceed 50–60% [39]. In this context, mHealth can build products that act as a complementary treatment tool for these diseases and thereby set a standard for product innovation. Indeed, there is a sign that based on the concept of "beyond the pill" [40], pharmaceutical companies are trying to fuse drug development and digital technology and are considering building a business model of digital medicine [41] [42].

Additionally, the number of mobile medical apps being cleared by the FDA has been increasing since 2010 in the United States. I confirmed 189 products

approved by FDA as of 2017, however mHealth that is approved as a medical device in Japan is only one product of Allm's Join as of September 2019 [43]. The situation varies greatly from country to country.

It is important to build a doctor-patient relationship and nurse-patient relationship for delivering high-quality healthcare. Effective doctor-patient communication is a central clinical function and a central component in the delivery of healthcare [44]. Currently, the three main goals of doctor-patient communication are creating a good interpersonal relationship, facilitating the exchange of information, and including patients in decision making [45]. The relationship that is established between the nurse and the patient is essential for the delivery of quality nursing care [46]. In this context, communication involves more than the transmission of information; it also involves transmitting feelings, recognizing these feelings, and making the patients aware of their feelings have been recognized [47]. Doctors and nurses were the sole providers of information about a patient's health; however, mHealth enables patients to "send" information about their health to patients and doctors. In the near future, mHealth can help doctors and nurses to suggest personalized care to their patients with functions of analytics and prediction and suggestions based on the collected real-time data.

3.5.2. Company and Industry Platform

The United States occupies the first place in the worldwide medical devices market in terms of both the market size as well as the number of manufacturers (approximately 6,500 companies) [48][49][50]. Even though our observation is limited to the universe of products approved by the FDA, our observation foresees that the United States will be a global hub of commercializing innovative mHealth products sustained by its industrial ecosystem where R&D for pharmaceutical and medical products also works as an R&D platform for innovative mHealth products by providing new entries or startups with credibility, assets and competencies through the coupling of technological and market development [51].

An mHealth technology provider can provide complementary assets [52] to pharmaceutical companies, thereby enabling the latter to increase the value of existing products and deliver better outcomes. For example, Raisin Personal Monitor developed by Proteus helps doctors and patients to monitor and improve drug adherence through an ingestible sensor and a feedback and monitoring patch. The Propeller System developed by Reciprocal Labs helps patients to understand what may be causing their symptoms. In these cases, pharmaceutical companies understand that their collaboration with a technology developer is necessary to

acquire solutions in the form of complementary assets. Pharmaceutical R&D provides a source of knowledge and serve as a platform of innovation for mHealth products and services developers. However, in the context of platform leadership [53], there is a possibility of a technology developer evolving into a platform leader and a pharmaceutical company assuming the role of a complementor.

3.5.3. Regulations toward Innovation

The influence of regulation on corporate innovation is either positive or negative depending on the characteristics of various industries and companies [53] and depending on the characteristics of technology [54]. For example, technological innovations in energy result from policies which stimulate adoption of widely available but under-utilized low-carbon technologies including both energy-efficient and renewable energy technologies and encourage the development and deployment of new technologies that are close to achieving a market presence [55] [56]. In the medical field, as an example of regulation contributing to the development of the industry, I can cite the measure to disseminate electronic medical record as an economic recovery measure after the Lehman shock by the Obama administration [57].

Such a consensus view of the influence of regulations on innovation is well translated in the present case. Following is a background to the recent increase in regulations (Figure 3-3). In 2012, FDA gave an approval to go forward with a regulatory framework for medical apps [58]; FCC approved its mobile body area network (MBAN) [58]; in 2013 FDA presented guidance and clarified regulatory targets. These regulatory reforms were supposed to significantly favor market expansion. The sharp increase of approvals between 2013 and 2014 turned to be a turning point in the mHealth market, together with indirect contributions of regulatory reforms or deregulations as shown in Figure 3.

Another important thing is The International Medical Device Regulators Forum (IMDRF). The IMDRF was conceived in February 2011 as a forum to discuss future directions in medical device regulatory harmonization [59]. It is a voluntary group of medical device regulators from around the world who have come together to build on the strong foundational work of the Global Harmonization Task Force on Medical Devices (GHTF), and to accelerate international medical device regulatory harmonization and convergence. The IMDRF aims to establish a common and integrated understanding of clinical evaluation and principles for demonstrating the safety, efficacy and performance of Software as a Medical Device (SaMD). The charter of the Working Group (WG) is to develop guidance that supports innovation

and timely access to safe and effective SaMD globally. The work is intended to identify commonalities, establish a common vocabulary and develop approaches for appropriate regulatory controls that promote prospective convergence in areas of advanced and innovative technologies in this topic area. The SaMD WG has published the documents (Table 3.6).

FDA integrated SaMD definition and risk-based criteria into regulatory Process and developed a The Software Precertification Program (Pre-cert pilot program) to increase efficiencies in SaMD approvals in July 2017[60]. Regulatory agencies and the payers are key players to make that determination of risk and coverage. IMDRF put out a classification called SaMD, “Software as a medical device”. IMDRF is a group of thirteen or so regulatory bodies that came together to create the “software as a medical device” criteria and framework. Japan is one of those countries. IMDRF put out some ideas around the clinical guidelines we must have, or the clinical validation, in addition to some of the quality. FDA has done implementation the Clinical Medical Device criteria as written into their process. They don’t have a specific focus yet though on digital therapeutics at this point. They consider all SaMD and they have not really broken it down into specific categories yet.

Regulations are also expected to arrest the deterioration particularly in the innovative field of mHealth. For instance, there are over a 1,000 apps in the consumer marketplace to help in treating depression [61] [62] whereas only 10 publications provide evidence in their support [63]. This may hamper the credibility of mHealth and hinder its market growth. Therefore, relevant standards of medical devices were clarified by enacting regulations at an early stage, thereby improving the confidence in the marketplace by ensuring the quality of the products and promoting industry growth.

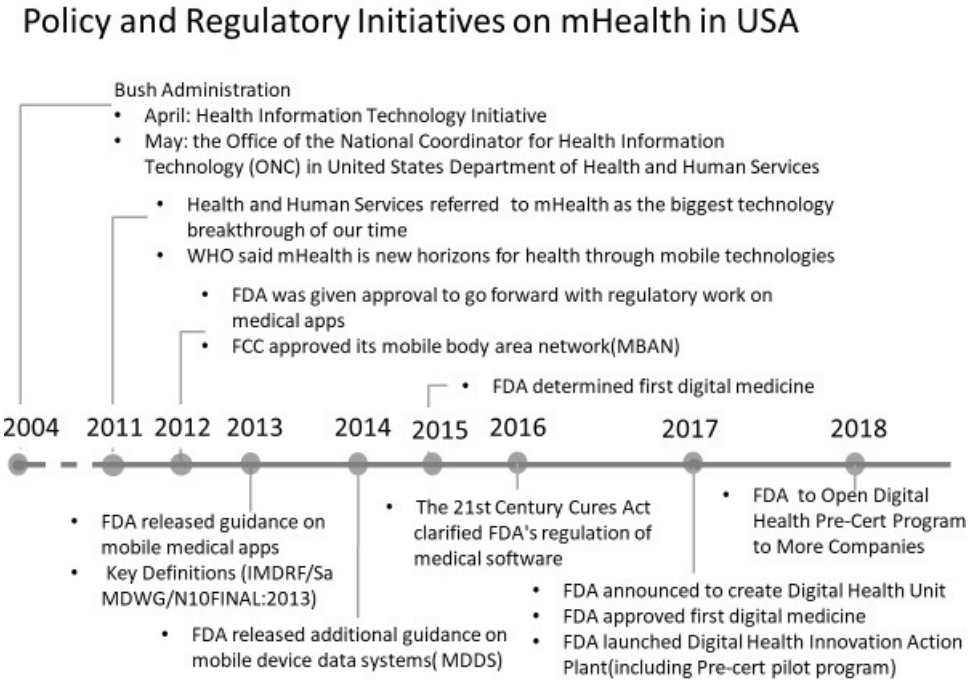

Figure 3-3. Policy and Regulatory Initiatives on mHealth in the United States

The historical transition of policy and regulatory initiatives on mHealth in USA was outlined from 2004 to 2018 with descriptions of selected key events.

Table 3-7. List of the documents IMDRF SaMD Working Group has published

Year	Name	Summary
2013	Software as a Medical Device (SaMD): Key Definitions (IMDRF/SaMD WG/N10FINAL :2013)	Key Definitions focuses on a common definition for when software is considered to be a medical device and a reminder of other key terms, some previously defined in Global Harmonization Task Force (GHTF) documents, with relevance to SaMD.
2014	Software as a Medical Device (SaMD): Possible Framework for Risk Categorization and Corresponding Considerations (IMDRF/SaMD WG/N12FINAL:2014)	Introduced a foundational approach, harmonized vocabulary and general and specific considerations for manufacturers, regulators, and users alike to address the unique challenges associated with the use of SaMD.
2015	Software as a Medical Device (SaMD): Application of Quality Management System (IMDRF/SaMD WG/N23 FINAL:2015)	Highlights elements of good software quality and engineering practices and reinforces medical device quality principles that should be appropriately incorporated for an effective SaMD QMS.
2017	Software as a Medical Device (SaMD): Clinical Evaluation, Final document (IMDRF/SaMD WG/N41FINAL:2017)	Describes a converged approach for planning the process for clinical evaluation of a SaMD. There is a valid clinical association between the output of a SaMD and the targeted clinical condition (to include pathological process or state); and the SaMD provides the expected technical and clinical data.

Note: the charters of the Working Group (WG) is to develop guidance that supports innovation and timely access to safe and effective SaMD.

3.6. Limitations

Although the present study focused FDA as the regulatory authority, observation in other regions is needed considering growing mHealth market worldwide [64]. Our findings are based only upon the information of approval by the FDA: further investigation is required to clarify and evaluate the commercialized status of mHealth products.

3.7. Conclusion

I examined the novelty of mHealth products approved by FDA (N=189) from both technological and market perspectives and found that that new product development in the existing medical market, that is, miniaturization and/or wireless technology formed the majority (N=171) whereas innovative products for diversification or new market development remained a minority (N=16 or 2, respectively). I revealed that the current mHealth industry is being shaped not by incumbents but by new entrants or start-ups that bring expertise in the field of information and communication technology, in particular, the minor but important area of innovation in collaboration with pharmaceutical and medical products companies. An mHealth technology provider can provide complementary assets to pharmaceutical companies, thereby enabling the latter to increase the value of existing products and deliver better outcomes. However, in the context of platform leadership [52], there is a possibility of a technology developer evolving into a platform leader. Finally, I discussed the significance of regulatory guidance and control for the growth of the mHealth market through a time course observation of regulations implemented in the United States and their effect on product entry.

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CHAPTER 4. THE IMPACT OF MHEALTH ON EXISTING MEDICAL SYSTEMS

4.1. Introduction

In this section, I focus on the paradigm innovation of mHealth as per the 4Ps innovation model. In chapter 3, I revealed that the current mHealth industry is being shaped, not by incumbents, but by new entrants or start-ups that bring expertise in the field of ICT in particular, a minor yet important area of innovation in collaboration with pharmaceutical and medical products companies [1]. I also found significant differences between the characteristics of the companies in the new product development quadrant and the characteristics of the companies in the other two quadrants [1]. The former group is composed of several companies that operate on a wider geographical spread, with a portfolio of multiple established products and aiming at incremental innovation based on their proprietary enabling technology assets such as the telemedicine platform or wireless mobile technology. Conversely, companies under diversification were established after 1996 and are based in the United States, operating with 18-150 employees. Furthermore, the founders of four prominent companies in this field—Welldoc, Proteus, GI-Logic, and Neurometrix—are medical doctors. Additionally, the number of mobile medical apps being cleared by the FDA has been increasing since 2010 in the United States. I also confirmed 189 products approved by FDA as of 2017, however only one mHealth product in Japan, Allm's "Join," was approved as a medical device in September 2019 [2]. I consider the sharp increase of approvals between 2013 and 2014 to be a turning point in the mHealth market, together with indirect contributions of regulation.

From examining these findings, I consider mHealth's paradigm innovation from the perspective of the relationship between innovation and regulation to identify why this situation arose. Along with the emergence of innovation in the regulated industry of medical care, the emergence of mHealth will be examined from various perspectives, focusing on what makes it different from drug and medical device innovations. The relationship between industry innovation and regulation is investigated through interviews, and paradigm innovation in mHealth is considered based on the facts of this relationship to clarify the impact of mHealth on existing healthcare (especially for signs of change and tension relationships among stakeholders, including quality, cost, and access to medical care).

4.2. Related studies

4.2.1 Innovation in Paradigm

Paradigm innovation was originally defined as “changes in the underlying mental and business models which frame what the organization does” by Tidd and Bessant [3] [4] [5]. This literature advises that paradigm innovation can be triggered by many different sources, from new technologies, the emergence of new markets with different value expectations, and new legal rules of the game, to changes in environmental conditions. It also stated that the point of business model innovation is to explore “how value is created and captured, and by whom” [5].

Rickards (1999) states, “Today the term paradigm’ has found its way into the vocabulary of organizational management, in such terms as “paradigm switch” and “paradigm breakthrough.” These expressions are broadly taken to imply that a traditional belief system, the old paradigm, has been replaced by a new way of understanding, a new paradigm” [6]. Thomas Kuhn (1970) introduced the concept of paradigm shift as a “fundamental change” in the core concepts, values, and practices of a scientific community or discipline [7]. Similarly, paradigm innovation both drives and is informed by a “shift” that may already be happening.

Francis and Bessant (2005) classified paradigm innovation into two types [2]. One is an inner-directed paradigm, that is, an innovation capability that targets organizational values and people management policies. The other is innovation in outer-directed paradigms (business models), that is, innovations of paradigms related to business models (a system of coherent, comprehensive, explicit and/or implicit constructs used by managers to understand their firm and shape its development). There has been growing attention on how innovation creates and captures value—the so called the “business model innovation” [8-12]. A business model should be able to link two dimensions of firm activity: value creation and value capture [12]. Value creation and capture are linked by what is sometimes called “value delivery” [8]. According to Teece (2010), “business model” defines the way the company creates and delivers value to customers and then captures a portion of this value to make profit and grow [13]. Organizations that pursue this type of innovation develop novel value-creation architectures and original revenue models, more than focusing just on new products or new services.

Tidd (2009) gave these examples of paradigm innovation [5]:

- Servitization: the bundling of products and services. For example, AI connected home automation such as Amazon Echo and Google Home.

- Ownership to rental: for example, music and video streaming platforms such as Spotify, Netflix and car-sharing clubs.
- Offline to online: internet-enabled substitution of physical encounters with virtual ones. For example, retail shopping and gamification.
- Mass customization, personalization, and co-creation: new technologies and a growing desire for customization enable the creation of not only personalized products and services but also platforms on which users can engage and co-create. For example, from toys (e.g., Lego), to clothing (e.g., Adidas)

I defined paradigm innovation as "changes in the underlying mental and business models that frame what the medical system adopts." Applying paradigm innovation in mHealth can mean influencing the existing business model of medical system by introducing mHealth. The value of healthcare provided by each stakeholder varies. For example, physicians provide therapy, hospitals provide medical service, pharmaceutical companies provide medicine for diagnosis and therapy, and medical equipment companies provide medical instruments for diagnosis and therapy. In this research, I examined paradigm innovators in mHealth who improve healthcare, compared to pharmaceuticals and medical devices, and the impact of mHealth in terms of both inner-directed and outer-directed paradigms in medical systems.

Since the healthcare sector has many stakeholders and complex relationships, there is no clear distinction between inner-directed paradigms and outer-directed paradigms. Rather, these two are interrelated. Based on this premise, I examined the paradigm of mHealth from two perspectives—inner directed paradigm and outer-directed paradigm. I defined inner-directed paradigm as the impact of mHealth on communication between physicians and patients in the healthcare delivery and consumption field, and outer-directed paradigm as the impact on how mHealth is developed and delivered to patients as a medical service.

With regard to mental models, the original literature of Tidd and Bessant (2009) does not provide a clear definition. The concept of mental models has been explained by theorists in various fields [14] [15]. In this study, we used the definition of Senge (1990) of mental models for use in organizational management [16]. Senge (1990) describes mental models as assumptions, generalizations, pictures, and images that are deeply rooted in our minds and have the ability to influence how we understand the world and our actions [16]. He also states that mental models are important for understanding individual knowledge building and behavior [16]. Based on this, I defined the changes in mental models in this study

as "How the emergence of mHealth affects medical assumption, and how changes in these assumptions affect the behavior of each stakeholder."

4.2.2 Regulation and Innovation

Regulations include legislation itself, as well as administrative supervisory policies, guidelines, administrative interpretations, and the rules of self-regulatory organizations accumulated over time based on these regulations [17]. Regulations have two sides: one which prevents serious adverse effects to the rights, safety, and lives of citizens [18][19], and the other that restricts innovation and causes a chilling effect [20], as well as opportunity loss. The maintenance of an appropriate balance between regulation and industry innovation, and the methods of realizing the purpose of regulations change with the progression of the technology of the age and society. Thus, it is necessary to discuss regulations that reflect the changes in the structure of society and industry [17,20- 22]. Technological innovation is conventionally seen as outpacing regulation, which usually "lags behind" innovation. There is a need for a new framework to change "Innovation first/regulation after" to "co-development of regulatory arena and novel technology" [21][22].

The influence of regulation on corporate innovation is either positive or negative depending on the characteristics of various industries and companies [23], and on the characteristics of technology [24]. For example, energy technology innovations resulted from policies that stimulate the adoption of widely available, but under-utilized, low-carbon technologies (including both energy efficient and renewable energy technologies, and encourage the development and deployment of new near-term technologies that are close to achieving a market presence [25][26].

In the medical field, as an example of the regulation contributing to the development of the industry, there is the "fast track" program by the FDA for drug approvals. In 1988, the FDA formalized the "fast track" designation, which permitted approval of drugs treating life threatening or severely debilitating diseases after a single phase 2 study [27]. There was a significant increase of 2.6% per year in the number of expedited review and approval programs granted to each newly approved agent, and a 2.4% increase in the proportion of drugs associated with at least one such program [28]. Another example is the resolution to disseminate electronic medical records as an economic recovery measure in response to the "Lehman shock," by the Obama administration [29]. The Obama administration implemented aggressive and expensive plans rooted in the former

president's belief that EHRs are crucial to healthcare modernization and cost containment [30].

Obamacare's incentive scheme was strikingly effective. In 2016, 96 percent of hospitals across the country had adopted EHRs. In 2009, before the ACA had been passed, only 12 percent of hospitals had adopted them, reporting up-front cost and maintenance expenses, uncertain return on investment, and inconsistent IT systems as the biggest barriers to adoption [31]. Another example is the expedited approval system for regenerative medical products in Japan. The Japanese Diet promulgated "The Act on the Safety of Regenerative Medicine (ASRM)" and "The Pharmaceuticals and Medical Devices Act (PMD Act)" in 2013 in order to reform the pharmaceutical and medical regulation related to regenerative medicine. This system was launched to speed up the delivery of treatments to patients and spur innovation of regenerative medical products. The revised law defined this as "estimation of efficacy" [32][33].

The intention of schemes to influence and regulate the ground and air transportation, financial services, telecommunications, and healthcare industries in the interest of the public evolves through three stages [18]: (i) subsidizing the establishment of the industry, (ii) stabilizing and strengthening the companies involved, by ensuring fair and equal access to their products and services and assuring consumers that their products are safe and effective, and (iii) encouraging competition to reduce barriers.

In the US medical industry, much of the government's regulatory focus is on ensuring that providers and products are safe and effective. When medicine is in the intuitive realm, the best mechanism for accomplishing this is to regulate who can provide care. Regulatory focus is on the inputs or resources used in the process, primarily the training and qualifications of the doctors who provide the care. A key reason that changes in regulation consistently lag behind medical progress is that losses of the side destroyed by the change in regulations are large, so the regulations that were originally intended for patients are now for their own benefit [18].

Christensen's (2009) research stated that the reformers usually lose head-on battles to deregulate what is regulated. Those who directly appealed to the government to change regulations to cause disruptive innovation are either left to wait for the law to change the regulations, or the idea itself is rejected. On the other hand, those disruptors that successfully dismantled the regulations that stood in their way succeeded by circumventing the regulation through innovating in a disruptive market that was beyond the regulators' reach or was peripheral to

their vision. Regulations ultimately change in reaction to innovators' success in those markets, they rarely change to enable disruptive success [18].

The maintenance of an appropriate balance between industry innovation and regulation, and methods of realizing the purpose of regulation change with the progression of the technology. Thus, it is necessary to discuss regulations that reflect the changes in the structure of society and industry. For example, if we do not create a basic framework for regulation of entry, regulation of behavior, and supervision regime in fields such as virtual currency and activity in space, we will have difficulties creating the necessary competitive environment and maintaining a sustainable business environment. This would result in the promotion of innovation through the creation of legislative regulation, making them apt examples of how regulations made to suit the historical background of the situation that can promote innovation [17].

In 2011, the International Medical Device Regulators Forum (IMDRF) was conceived as a forum to discuss future directions in medical device regulatory harmonization [34]. In 2012, the FDA gave an approval to go forward with a regulatory framework for medical apps [35]. Then, in 2013, the Federal Communications Commission (FCC) approved its mobile body area network (MBAN) [35]. FDA presented guidance and clarified regulatory targets [36]. These regulatory reforms were supposed to significantly favor market expansion. The sharp increase of approvals between 2013 and 2014 became a turning point in the mHealth market, together with indirect contributions of regulatory reforms or deregulations as discussed in chapter 3. For this research, I further explore the relationship between regulations and mHealth through interviews.

4.3. Materials and methods

4.3.1. Interviews

I interviewed four peoples to cover the four aspects of product, process, position, and paradigm of mHealth. The criteria used for selecting interviewees are as follow:

- A person who established a startup company with mHealth,
- A person who is working with regulators or payers in mHealth,
- A person who is working in a hospital in a position to choose medical devices or medical systems,
- A person who is working in a pharmaceutical company planning clinical studies with medical devices,

As a result, I interviewed the people below:

- Dr. George Savage, CEO, Proteus Digital Health;
- Ms. Megan Coder, Executive Director, Digital Therapeutics Alliance;
- Mr. Arthur Hermann, Principal Strategic Consultant, Kaiser Permanente;
- Dr. Emilio Merlo Pich, Executive Medical Director in Clinical Science, Neurology, Takeda Pharmaceutical Company.

I conducted semi-structured interviews based on several question items (see Appendix).

4.3.2. Research on regulations

I investigated regulation related to mHealth in the US using the databases from the FDA, Health IT.gov (the official website of The Office of the National Coordinator for Health Information Technology), and HHS.gov (U.S. Department of Health & Human Service).

4.4. Results

4.4.1. Relationship between regulation and innovation in mHealth

The US government is promoting healthcare ICT to improve the quality of care and reduce costs. These form the core of federal law for healthcare ICT [37] (Table 4-1). These laws indicate the need for ICT and information in healthcare. There is a system of standardization such as Health Level (HL7) for information utilization ahead of ICT adoption. Hospitals and other healthcare provider organizations typically have many different computer systems used for everything, from billing records to patient tracking [38]. All these systems should communicate with each other (or "interface") when they receive new information or when they wish to retrieve information, but not all do so.

HL7 and its members provide a framework and related standards for the exchange, integration, sharing, and retrieval of electronic health information. These standards define how information is packaged and communicated from one party to another, setting the language, structure, and data types required seamless integration between systems. HL7 standards support clinical practice and the management, delivery, and evaluation of health services, and are recognized as the most commonly used in the world [39].

As previously mentioned, in 2011, The IMDRF was conceived as a forum to discuss future directions in medical device regulatory harmonization [34]. The IMDRF is a group of thirteen or so regulatory bodies that came together to create the “software as a medical device” (SaMD) criteria and framework. Japan is one of those countries. The IMDRF aims to establish a common and integrated

understanding of the principles for clinical evaluation and the demonstration of the safety, efficacy, and performance of SaMD [34]. The charter of the Working Group (WG) includes providing guidance that support innovation and timely access to safe and effective SaMD globally. The work is intended to identify commonalities, establish a common vocabulary, and develop approaches for appropriate regulatory controls that promote prospective convergence in advanced and innovative technologies in this topic area. The SaMD WG has published relevant documents for this purpose. The IMDRF put out some ideas around the necessary clinical guidelines or clinical validations, in addition to those of quality. The FDA has completed the implementation of the Clinical Medical Device criteria as written into their process. However, they do not have a specific focus on digital therapeutics at this point yet. The FDA integrated the SaMD definition and risk-based criteria into regulatory and gave an approval to go forward with a regulatory framework for medical apps in 2012 [35]. The FCC approved its MBAN [35]. The FDA presented guidance and clarified regulatory targets in 2013 [36].

The FDA launched a Pre-cert pilot program on July 27, 2017, as part of the agency's Digital Health Innovation Action Plan [40]. The outline of the plan clarifies the provisions of medical software in the Federal Law of 2016 (21st Century Cures) and add expertise to the digital healthcare sector. The FDA sought to promote digital health innovation while continuing to protect and promote public health by launching a pre-approved pilot program. The pilot participants represented a wide range of digital healthcare companies and technologies, including small startups and large companies, high- and low-risk medical device software products, medical device manufacturers, and software developers [40]. Selected participants are shown in Table 4-2, and more than 100 companies applied the program [40]. Several factors were considered in selecting participants, including company size, quality and organizational performance, clinical focus, and product risk profiles. The FDA streamlines the regulatory review process that helps encourage the innovation of digital health technologies. This innovation, and the associated rapid iterative cycles, has the potential to improve patient outcomes and product performance. While the FDA's goal with Pre-Cert is to regulate digital health technologies in a way that fosters innovation, the model the agency is piloting is firmly rooted in protecting patient safety.

Ms. Megan Coder, Executive Director of Digital Therapeutics Alliance argued that "regulatory agencies are key players in making that determination of risk. The FDA is eager to support and develop the digital therapeutic space, and they are doing a very good job with trying to figure this out. This all goes back to the

IMDRF. They are going to be important." She continued to comment on the Pre-Cert pilot program. "This proposed approach aims to look first at the software developer or digital health technology developer, rather than primarily at the product, which is what we currently do for traditional medical devices. This is because software products can be adapted to respond to glitches, adverse events, and other safety concerns quickly. The FDA is working to establish a regulatory framework that is equally responsive when issues arise to help ensure consumers continue to have access to safe and effective products. In the Pre-Cert program, the FDA is proposing that software products from pre-certified companies would continue to meet the same safety and effectiveness standard that the agency expects for products that have followed the traditional path to market."

The Interstate Medical Licensure Compact (IMLC) also changes in line with the penetration of mHealth. In the United States, medical licenses are under the jurisdiction of the state government, and the level of authority varies from state to state. The IMLC mission is to increase access to healthcare for patients in underserved or rural areas, allowing them to easily connect with medical experts using telemedicine technologies [41]. While making it easier for physicians to obtain licenses to practice in multiple states, the IMLC strengthens public protection by enhancing the ability of states to share investigative and disciplinary information. Physicians can provide remote care to patients in other states through IMLC, and this type of telemedicine is expanding.

The FDA came up with various approaches when they first introduced Proteus Digital Health's ingestible sensor technology. There was no prior category at the FDA for this device; it was too innovative. Dr. George Savage from Proteus Digital health said, "The FDA has been supportive of what we're doing. The FDA, on the medical device side, and the Center for Devices in Radiological (CDRH), under Doctor Gottlieb's leadership at the FDA, work to modernize the approach to approving software. Bakul Patel runs the digital health center of excellence at the FDA and he has done a very good job at bringing software regulation into a more modern context where regulation is lighter and can move at the speed required to have up-to-date products that would run on a patient's mobile phone; so, very positive results there."

The digital medicine that Proteus Digital Health (along with its partner, Otsuka pharmaceutical) developed has very low risks; thus, premarket approval was not appropriate on the device side. What the FDA then did was to create a new "class two" category for the device, doing what is called the De Novo approval—an approval of a new class to device category, Hence, the subsequent devices were

cleared under 510(k), a premarket notification referring to their De Novo approval. In Proteus's case, drugs were approved according to the existing NDA process.

Its partner, Otsuka, has obtained a new drug application approval (an NDA approval) under what is called 505 (b) (2). 505 is the NDA portion of the FDA and various types of drug approvals are listed in that regulation, for example 505 (b)(1) and 505 (b)(2) [42]. 505(b)(1) is for a new molecular entity, a brand-new drug. The 505(b)(2) regulatory pathway is another type of NDA submission that can be used to obtain the approval of a new drug. This type of submission differs from the 505(b)(1) NDA in that the product in question contains similar active ingredients to a previously approved drug [43]. An example would be Abilify, a product that was already on the market, but has now had a sensor added to it, to make it a 505 (b)(2) drug. It is a type of NDA pathway for the combination of a drug with an ingestible sensor, where the two are built together in the factory, in Tokushima, and then shipped to the Unites States. There is also the abbreviated new drug application (ANDA) for generic drugs that falls under 505 (j). The 505 (j) application is an ANDA that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics and intended use, among other things, to a previously approved product—the reference listed drug [44].

In Japan, the "Pharmaceutical Affairs Law" was revised to the "Pharmaceuticals and Medical Devices Law" and came into effect on November 2014. In the past, only the software side of the industry was not regulated by the Pharmaceutical Affairs Law. Rather, it was regulated as part of hardware. However, under the Pharmaceuticals and Medical Devices Law, software can be distributed as a single unit and is regulated as a "medical device program" [45]. As of September 2019, the only mHealth product in Japan that has been approved as a medical device is "Join" by Allm [2]. In 2016, Allm's service, "Join," became the first of its kind to be recognized by the Ministry of Health, Welfare, and Labor for coverage within the National Health Insurance. Join is a communication app for medical professionals, designed by doctors for doctors. In case the ER team needs information fast, Join provides it at the tap of a screen. By enabling connections with PACS (picture archiving and communication systems) and other systems, Join allows professionals to share clinical medical information in order to achieve greater diagnostic precision and better patient care.

Table 4-1. Core federal law for healthcare ICT in the United States

Year	Name	Summary
1996	The Health Insurance Portability and Accountability Act (HIPAA)	Protects health insurance coverage for workers and their families when they change or lose their jobs, requires the establishment of national standards for electronic healthcare transactions, and requires the establishment of national identifiers for providers, health insurance plans, and employers.
2009	The Health Information Technology for Economic and Clinical Health (HITECH) Act	Provides the U.S. Department of Health and Human Services (HHS) with the authority to establish programs to improve healthcare quality, safety, and efficiency through the promotion of health IT, including electronic health records creation, as well as private and secure electronic health information exchange.
2010	The Affordable Care Act	Establishes comprehensive healthcare insurance reforms that aim to increase access to healthcare, improve quality, lower healthcare costs, and provide new consumer protection.
2012	Section 618 of the Food and Drug Administration Safety and Innovation Act (FDASIA)	Provides recommendations on an appropriate, risk-based regulatory framework for health IT, including medical mobile applications that promotes innovation, protects patient safety, and avoids regulatory duplication. The Health IT Policy Committee formed a FDASIA workgroup and issued recommendations to ONC, FDA, and the FCC.

Note: descriptions of selected core federal law for healthcare ICT in the United States. These were signed into law between 1996 and 2012.

Table 4-2. Company of the Software Precertification program

Company name	Headquarter	Founded	Categories
Johnson & Johnson	New Brunswick, New Jersey	1886	Healthcare, Health Diagnostics, and Information Technology
Roche	Basel, Switzerland	1896	Biotechnology, Health Diagnostics, and Pharmaceutical
Samsung Electronics	Seoul, South Korea	1969	Electronics, Hardware, Manufacturing, Mobile, Mobile Devices, and Software
Apple	Cupertino, California	1976	Consumer Electronics, Electronics, Hardware, Mobile Devices, Retail, and Software
Fitbit	San Francisco, California	2007	Cloud Computing, Fitness, Healthcare, Personal Health, and Wearables
Tidepool	Palo Alto, California	2011	Gamification, Gaming, and Online Games
Pear Therapeutics	Boston, Massachusetts	2013	Biotechnology, mHealth, and Therapeutics
Verily	Mountain View, California	2015	Biotechnology, Data Mining, Healthcare, Information Technology, and Personal Health
Phosphorus	New York, New York	2016	Biotechnology, Genetics, and Healthcare

Note: descriptions of selected companies for the software pre-certification program. These pilot participants represent a wide range of companies and technology in the digital health sector, including small startups and large companies, high- and low-risk medical device software products, medical product manufacturers and software developers. The table was created by the author based on information from the FDA [40].

4.4.2. The Impact of mHealth on existing medical systems

In the US, with the trend of moving patient care from hospital to home, mHealth has been found to help physicians make better decisions and provide effective feedback based on patient data, especially with respect to chronic diseases. Dr. George Savage of Proteus Digital health stated that “mHealth supports building objective feedback and measurement into drug therapy between physician and patient. mHealth can help patients take their drugs better and help physicians make better decisions.” Mr. Hermann of Kaiser Permanente described that “our goal is to move more and more things to the home from the hospital. mHealth has become very important in terms of managing and tracking chronic diseases between physicians and patients.” Dr. Emilio Merlo Pich of Takeda Pharmaceutical also said that monitoring information about adverse events and vital changes over time with mHealth helps physicians, and is valuable in drug development. The interview results indicated that the contribution of mHealth to medical treatment, inherent in its technical characteristics, includes enabling the real-time monitoring of patients and their conditions, with little burden to the patient.

In addition, I found a new role of physicians in mHealth. Welldoc, Proteus, and GI-Logic, who are developing products classified as "Diversification" in Chapter 3 are companies founded by medical doctors [1]. Among them, Proteus is the first company in the world to receive digital medicine approval. The mHealth industry is still so small that there is no large sample size to pull medical entrepreneurs in mHealth from. However, Dr. Savage, Mr. Hermann, and Dr. Merlo Pich stated that physicians also hold the post of entrepreneur and play important roles in mHealth.

Dr. George Savage stated that “there are many physicians who become entrepreneurs and that medical doctors are moving into the medical mobile app space. I think it is fair to say that the IT side of the medical arena has drawn a lot of attention and many new entrances because it is a new field, which means there are no established incumbents that dominate it. Whenever there is something that is brand new, there is a lot of excitement, innovation, and an opportunity to create something. I think it is fair also to say, though, that many digital health companies have not grown as quickly or have received the adoption of their products as much as they would have expected. Furthermore, it has been relatively more challenging to generate significant revenues and significant company growth in most digital health companies and I think that is related to the complexity of the US health system as its evolution over the last ten years.”

Mr. Arthur Hermann, the Principal Strategic Consultant of Kaiser Permanente, observed that "the most important players are physicians because they have to be able to accommodate information flow in the hospital. In the field of digital health, including mHealth, that combination of physicians and the technology people are very important for the maturity of technology in hospitals or healthcare organizations. I think that doctors and entrepreneurs are the best people for implementing new technology in healthcare."

Smartphones dramatically improve the real-world effectiveness of pharmaceutical therapy. Physicians do not know whether patients are taking their drugs appropriately and, therefore, do not know whether to revise the diagnosis or advice the patient to do better adhering to their treatment when issues arise. Given this, mHealth helps physicians make better decisions based on patient data and can help patients take their drugs better by providing feedback and measurement in drug therapy. Dr. Emilio Merlo Pich, Executive Medical Director in Clinical Science, Neurology, at Takeda Pharmaceutical Company, cited the Cleveland Clinic as an example, as doctors at the Cleveland Clinic use advanced technologies [46]. For example, the clinic uses a smartphone electrocardiogram (ECG) monitor to record a patient's heartrate and condition instead of the patient getting one ECG every few months through a doctor's appointment [47]. Mr. Arthur Hermann introduced digital strategy at Kaiser Permanente. He said, "Our goal is to move more and more things to the home from the hospital. mHealth has become very important in terms of managing chronic diseases, but it just depends on what the disease is. However, if we can kind of do a continuous monitoring, or it doesn't have to be continuous, but maybe once a day we get some input, we can track, we can understand progress, we can potentially get warnings when things are going wrong."

Kaiser Permanente is a completely electronic company. They have one of the largest messaging infrastructures at the heart of their electronic systems, with all of the messaging streams as the veins and arteries [48]. Their medical device integration project, which they are just completing, automatically updates their EMR with vitals from the machines. They use Health Language 7 (HL7) as their standard messaging format, because HL7 is the international standard for health information messaging [39]. They also use Systematized Nomenclature of Medicine (SNOMED), another data point. SNOMED clinical terms is a global language for health uniting systems enabling them to communicate and understand one another [49].

The use of ICT in medical care is changing the organization of medical institutions. With the growing need for ICT and information in healthcare, executives at leading health systems and hospitals are increasingly adding chief digital officers (CDOs) to their senior leadership teams. According to a survey from PricewaterhouseCoopers in early 2016, only 6 percent of the top 1,500 global companies had CDOs, at that time [50]. However, the CDO is an emerging and fast-growing executive role in healthcare as hospitals and health systems are looking for key leaders to manage their overall digital strategy and the consumers' digital experience. Ascension, one of the largest U.S. healthcare systems with 153 hospitals, hired Eduardo Conrado as its first CDO, charged with steering the health system's digital strategy and accelerating digital initiatives [51]. Conrado comes to Ascension from Motorola, where he recently served as the chief strategy and innovation officer. Similarly, Kaiser Permanente hired Richard "Dick" Daniels as Chief Information Officer and Executive Vice-President [52], and Thomas Jefferson Health hired Neil Gomes as CDO and Executive Vice President for Technology Innovation and Consumer Experience [53].

Pharmaceutical companies are also exploring opportunities in mHealth, in both clinical trials and therapy. Dr. Emilio Merlo Pich said, "Building new clinical trials with mHealth is very important because they will be based on the willingness of people to participate and to share the data that will be available. This leads to building a strong statistical package for foreseeing the signal of efficacy. Regarding the technology selection criteria for clinical trials, a higher probability of seeing a signal of an effect drug is important. Another important aspect is to reduce the cost and burden experienced by the involved subject."

Otsuka Pharmaceutical developed digital medicine with Proteus Digital Health and became the first company in the world to have gained FDA approval on a fully digital drug [54]. It is not Otsuka only, however. There are many other examples between pharmaceutical and mHealth companies such as GlaxoSmithKline and Propeller Health's partnership to develop mHealth for asthma and chronic obstructive pulmonary disorder (COPD) [55], and Roche, which has acquired mySugr to form a leading open platform for digital diabetes management [56].

In the reimbursement system, a direct relationship does not exist in the United States. "FDA-approved" does not mean a reimbursement by payers. The company that developed the product has to approach every single payer individually. Currently, digital therapeutics is only available in the private sector. In the public sector, there is Medicare, which mostly focuses on those who are older

than sixty-five years, and Medicaid, which is targets people who are under the poverty line [57][58] (Figure 4-1). Some Medicaid payers are starting to cover companies with very small numbers, like WellDoc. The Medicare side has not yet considered this; they should go through the private payer system as opposed to the public payer system in the US. Their prices are generally recommended by the company. Price setting is a very complicated system as they first have to propose a price and then wait for the negotiations to start in the US.

Although only a few economic studies on mHealth exist, several systematic reviews have been conducted on the topic. One such review is on mHealth technologies for cardiovascular diseases (mainly heart failure and stroke) [59]. Of the fourteen studies in existence, five are on video conferencing, another five are on remote monitoring, and the rest are on SMS transmissions, phone support, mobile apps, and wearables. Because of the cost-effectiveness analysis, six studies showed cost reduction and eight studies showed that the incremental cost-effectiveness ratio (ICER) [60] was generally acceptable at around USD 50,000 / Quality-Adjusted Life Years (QALY) [60]. Researchers reported that mHealth interventions were cost-effective, economically beneficial, or cost saving at base case.

One other study is based on a cost-effectiveness analysis comparing cognitive behavioral therapy (CBT) for anxiety disorder using mHealth with conventional face-to-face cognitive behavioral therapy and maintenance therapy [61]. mHealth interventions centered on eight cognitive behavioral self-study programs and individual professional messages with a background in psychology. Compared with conventional face-to-face cognitive-behavioral therapy and maintenance therapy, it was superior in terms of cost-effectiveness because it reduced costs and improved QALY.

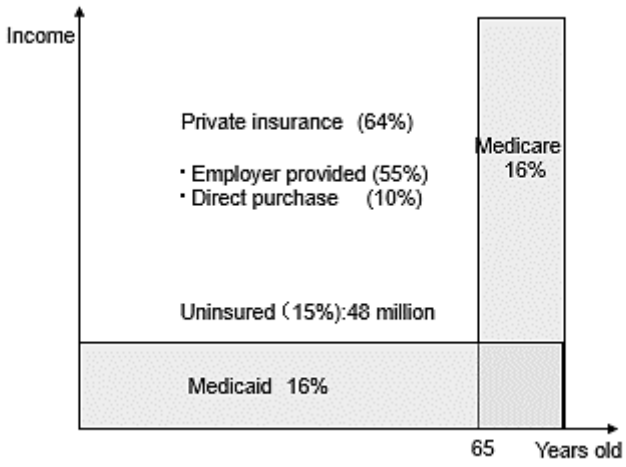

Figure 4-1. Health Insurance Coverage in the United States

US government runs two programs, Medicare and Medicaid. These programs are operated and funded by different parts of the government and primarily serve different groups. The figure was created by the author based on the information from [57][58].

4.5. Discussion

4.5.1. ICT Player

I analyzed two aspects of mHealth, inner-directed paradigm and outer-directed paradigm, in order to analyze the factors that cause paradigm innovation. Regarding an inner-directed paradigm innovation, Abrahamson, calls these “administrative technologies” [62]. I defined inner-directed paradigm of mHealth as the impact of mHealth on communication between physicians and patients in the healthcare delivery and consumption field. From examining the findings about inner-directed paradigm innovation, ICT players enable the daily monitoring of patients for personalized care in inner-directed paradigms of mHealth. Proteus Digital Health developed Proteus Discover and got FDA approval. This is comprised of ingestible sensors, a small wearable sensor patch, an application on a mobile device and a provider portal. Once activated, Proteus Discover unlocks never-before-seen insight into patient health patterns and treatment effectiveness, leading to more informed healthcare decisions for everyone involved [63]. Proteus's innovation is the last mile of confirmation of a patient's medication adherence. Annual costings of medication non-adherence range from USD 100 to USD 290 billion in the USA [64]. Additionally, 10% of hospitalizations in older adults are attributed to medication non-adherence [65] [66] with the typical non-adherent patient requiring three extra

medical visits per year, leading to an increase of USD 2000 in treatment costs per annum [67]. As. Mr. Arthur Hermann mentioned, the aim is to move disease management from hospitals to the home. The same is true of pharmaceutical companies' clinical trials. mHealth eliminates space constraints, building objective feedback and measurement into drug therapy to help patients take their drugs better, and helps physicians make better decisions. mHealth can allow patients to become "senders" of information on their health status to the doctors, instead of doctors always being the informers. This is an example of mHealth as an inner-paradigm innovation in healthcare.

mHealth is not the only innovation in health, but when considering the impact of ICT on organizations in general, the deployment of CDOs in hospitals is worth mentioning. The increase of CDOs in hospitals is a result of the recognition, by medical institutions, of the importance of both medical care provision and technology and information management. However, several valid findings from systematic reviews of mHealth's economics, specifically regarding healthcare quality, have been reported. Nonetheless, I believe that verification is still necessary.

4.5.2. Interactive regulator

Another innovator in mHealth is the FDA. I define outer-directed par adigm as the impact on how mHealth is developed and delivered to patients as a medical service. When I look at the business model in terms of how inn ovation creates and captures value, the FDA, as the regulatory authority, is t he leader in changing the business model from examining my findings.

Technological innovation is conventionally seen as outpacing regulation, in other words, regulation usually "lags behind" innovation. This trend is expressed as "Innovation first/regulation after" [21]. A new framework is needed to change "Innovation first/regulation after" to "co-development of regulatory arena" [21][22]. Furthermore, it is generally agreed today that regulations ultimately change in reaction to innovators' success and rarely change to enable disruptive success [18]. From examining the findings, the FDA is changing their mental model to promote innovation as an "interactive regulator" in the field of mHealth. In the past, drugs and medical devices were considered to fall under the category of existing drugs or medical devices, requiring a long development period and not requiring any modification of the products after their launch. However, with the advent of mHealth, the FDA changed the approval process by changing its assumptions in anticipation that it would not fall into the category of drug or medical device, and

that some modifications to the product after launch would be developed, as with drugs or medical devices, in the short term.

I described the relationship between core federal law for healthcare ICT, regulatory initiatives in the United States, and the number of mHealth products approved by FDA in Figure 4-2. One is a systematic healthcare policy that has been in place since 1996 in the US. The US government developed core federal laws for healthcare ICT between 1996 and 2012. Based on these federal laws, the utilization of ICT in medical care, including EHR, is advancing. The diffusion of mobile phones and smartphone technologies are expanding the possibilities of mHealth. Today, mobile phones and smartphones have become essential components of our lives. Smartphones have been defined as "mobile telephones with computer features that may enable them to interact with computerized systems, send e-mails, and access the web" [68]. In 2018, the number of mobile phone users was 5.1 billion [69]. In addition, the number of clinical trials using mHealth began increasing after 2010 [70] and the number of clearances for mobile medical apps have been increasing since 2010 and doubled between 2013 and 2014 [1].

In 2011, the IMDRF started the discussion about SaMD for future directions in medical device regulatory harmonization. The IMDRF captured a trend of ICT, as well as clarified the definition of SaMD and the object of the regulation. The FDA then integrated the SaMD definition and the organization was given approval to go forward with regulatory work on medical apps. In addition to that, in 2012, the FCC approved its mobile body area network (MBAN). I consider the core federal law to have led to this sequence of events. It is assumed that the FDA captured the ICT trend and predicted the impact of mobile technology in healthcare based on the US healthcare policy. I believe that these results have contributed to the increase in the number of approvals. It seems that the sharp increase of approvals between 2013 and 2014 became the turning point in the mHealth market.

Furthermore, mHealth has benefitted from pre-cert programs, which now play a vital role. Pre-cert programs aim to streamline the regulatory review process to help encourage innovation of digital health technologies. The pilot participants represent a wide range of companies and technologies in the digital health sector, including small startups and large companies, high- and low-risk medical device software products, medical product manufacturers and software developers. It is a case of co-developing regulatory frameworks with small startups, large companies, and regulation. It is helps in ensuring that regulation changes to enable disruptive success with innovators. This is a new method to strike a balance between the speed of technological evolution and regulations. The rapid pace of advances in science and

technology has important implications for health and medicine. These breakthroughs may come with unintended and unforeseen consequences, with potentially important societal impacts. Policy makers must work together with other stakeholders, including industry, and academia to promote transparency concerning the use and development of new technologies. According to these results, it is thought that the FDA is an innovator in mHealth.

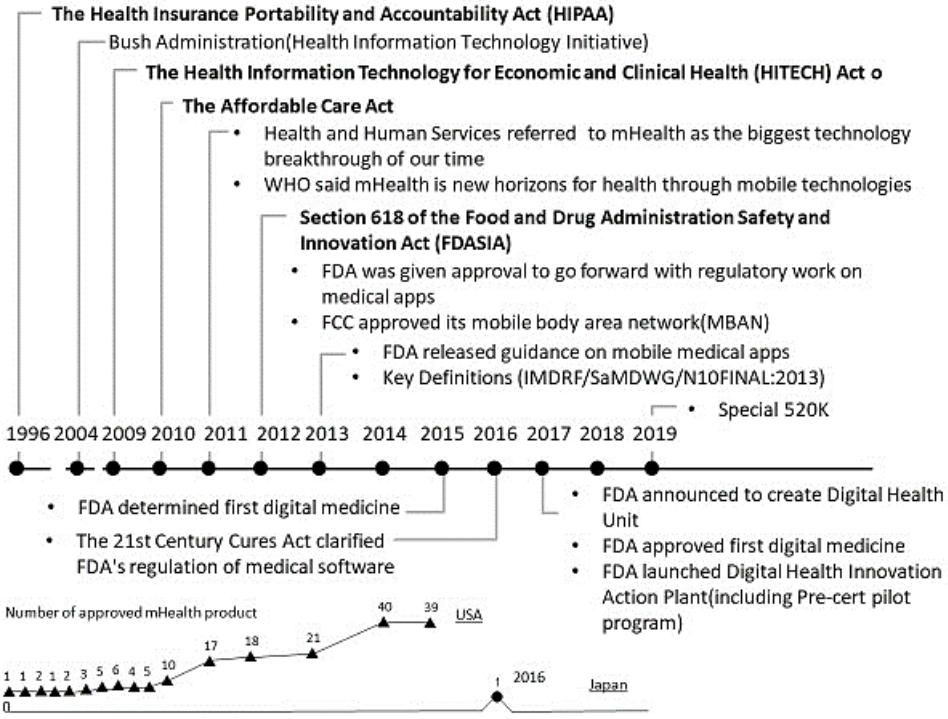

Figure 4-2. The relationship between core federal law for healthcare ICT, regulatory initiatives, and the number of mHealth products approved by the FDA in the US

The historical transition of core federal law for healthcare ICT, regulatory initiative in the United States and products approved by FDA from 1997 to 2015 analyzed in chapter 3.

4.5.3. Medical entrepreneur

The third innovator in mHealth is the medical entrepreneur, a term coined by Hacker [71] for medical doctors that start businesses. Welldoc, Proteus, and GI-Logic, who are developing products classified as radical innovation, are companies founded by medical doctors. These companies, established after 1996, are based in the United States and operate with 18-150 employees. Regarding their common points, apart from the fact that these entrepreneurs are medical doctors that have

started mHealth companies, there is nothing common between them in terms of the universities they graduated from or their majors. Although the mHealth industry is still so small that there is no large enough sample size to study, hence I have mentioned only three such samples, it is important to note that new players are entering this market rather than the existing medicines and medical devices sector.

Medical Doctors are said to have great potential as entrepreneurs [72] and during my interviews with them, Dr. Savage, Mr. Hermann, and Dr. Merlo Pich agreed with this sentiment. Based on the results of the interview, the reason behind this view is that physicians understand patient's needs and clinical issues better that anyone else. While the importance of ICT in healthcare is understood, there are hurdles and barriers to implementing them, and several studies on the difficulty, failures, and challenges of ICT adoption in healthcare have documented this [73] [74]. In the case of electronic health records, the main obstacles reported are costs of deployment, physicians' low IT literacy, lack of strategic planning for deployment, and difficulty in recruiting experienced IT personnel [75-77]. Lack of technical training and support from vendors has also been reported as barriers to physicians' adoption of EMR [78]. Because EMR systems were still relatively new to the market at the time of these studies, vendors were not qualified to provide the right services, and concerns arose that they would go out of business and disappear from the market, leading to lack of technical support and significant losses. In the case of E-Prescribing, barriers to adoption of technology are said to include previous negative experiences with technology, deployment costs, and changes or increases in workflow [79] [80]. Against this background, it stands to reason that medical entrepreneurs are better positioned to bridge the gap between healthcare and technology since they understand not only the needs of their patients, but also how they can fit into existing healthcare systems and workflows without increasing their workload.

Consequently, I consider medical entrepreneurs to also represent inner-directed paradigm innovators of mHealth, especially in terms of transforming communication between patients and medical doctors. For instance, since medical doctors capture patients' needs and create value through mHealth, medical entrepreneurs have the potential of being interpreters and fill the gap between patients, other medical doctors, and engineers. They can do this by using insight from their activities as doctors to gain understanding, and communicate this information to the company's engineers. Therefore, these doctors can guarantee the accuracy of products based on their medical expertise and can develop ways to support treatment based on their clinical experiences.

From examining the findings from my research, there are three reasons for

this. The first is that investment in digital health in the United States is increasing year-by-year [81]. Digital health companies raised a total of USD 4.2 billion across 180 deals through the first half of 2019. If this pace holds steady, the sector is on track to reach USD 8.4 billion by the end of 2019, and may even top the record-breaking annual funding total of the year 2018. As in 2018, a handful of USD 100 million, or more, mega deals are driving the overall trend [81]. The ICT side of the medical arena has drawn a lot of attention and new entrants because it is a new field. This is because new fields are inherently exciting since they do not have established and dominating incumbents and because of the opportunities they present in terms of innovation and the potential to create something great.

The second is that the US has a good entrepreneurial environment. The Wharton School of the University of Pennsylvania and market research firm Y & R have shown that, through their survey conducted on 80 countries around the world, the U.S. startup environment ranks third after Germany and Japan [82]. This survey considered 9 things: "adventure" "citizenship" "cultural influence" "entrepreneurial spirit" "an inheritance that is inherited" "influential persons" "openness of business" "power" "quality of life" and attributes that are relevant to entrepreneurs.

The third reason is the value of the data collected by mHealth. mHealth is a new modality of therapy following small molecules, biologics, and cell/gene therapies. An mHealth-powered solution can accurately convey data entered by a patient directly to the doctor. Data can be digitized and stored so that they can be stratified and divided into subgroups, potentially leading to precision medicine. Today, the utilization of digitized data in medical treatment attracts much attention. mHealth is a data entry point and is expected to provide new value in prevention, treatment, and disease management. As the number of stakeholders increases and the need for common rules across countries is anticipated, the findings of mHealth will become important.

4.5.4. Other stakeholders

Based on a survey of eight physicians in Japan, changes in the mental model of physicians due to mHealth were examined (data not shown). Although mHealth has not been introduced in clinical practice in Japan at present, many physicians responded that they would not hesitate to use mHealth if it is effective and safe, and would employ mHealth, as well as drugs and medical devices, if it were good to do so. In the clinical field, new drugs and medical devices are released daily and it is gradually becoming a matter of course to introduce new drugs and medical devices.

Therefore, it was suggested that at this point, mHealth is considered similar to the release of new drugs and medical devices. Since the ultimate goal of drugs and medical devices is to improve patients' lives and treatment experiences, mHealth has a similar purpose. As for its impact on medical care, many respondents said that mHealth is only a support tool for communication between physicians and patients since face-to-face consultation with patients is necessary for medical care. Given this, mHealth is not likely to change the mental model of physicians at this point.

As for changes in patients' mental models, since it was out of the scope of this study, I could not observe changes in patients' perceptions and attitudes about mHealth. However, based on the results of my empirical studies and interviews, mHealth has the potential to strengthen patients' sense of ownership in healthcare. It is said that although patients are the primary providers of treatment, there is a high tendency for patients to fail to accurately grasp their own symptoms or to leave the treatment to doctors. In this context, mHealth may change the patient's own involvement in treatment by giving them a sense of sharing treatment responsibilities with the physician.

4.5.5. Potential paradigm innovators in mHealth

Commercial barriers in healthcare are the most critical factors to consider compared to anything else in the industry. On the other side of these barriers, however, are regulations, which are necessary to ensure safety and effectiveness within the health industry. Assuming paradigm innovation in mHealth, the FDA and medical entrepreneurs are the potential paradigm innovators leading the change (Figure 4-3).

As rule makers, regulators create regulations and define industry rules; hence, they can play a vital role in paradigm innovations in healthcare. For example, concerning mHealth, the fact that the FDA and other companies are creating rules to take advantage of new technologies through dialogue is an example of a changing business model (or paradigm innovation). mHealth could be a good opportunity for an "interactive regulator" to take advantage of new technologies. Another paradigm innovation is evident in a new trend where medical entrepreneurs are entering the mHealth sector instead of existing pharmaceutical and medical device companies. These medical entrepreneurs led mHealth companies are able to capture data between patients and healthcare professionals that was previously unavailable to major pharmaceutical and medical device manufacturers. However, such data value delivery is not limited to patients and healthcare professionals, it also provides important insights for product development to pharmaceutical and medical device

manufacturers. This is a sign of business model changes within healthcare systems.

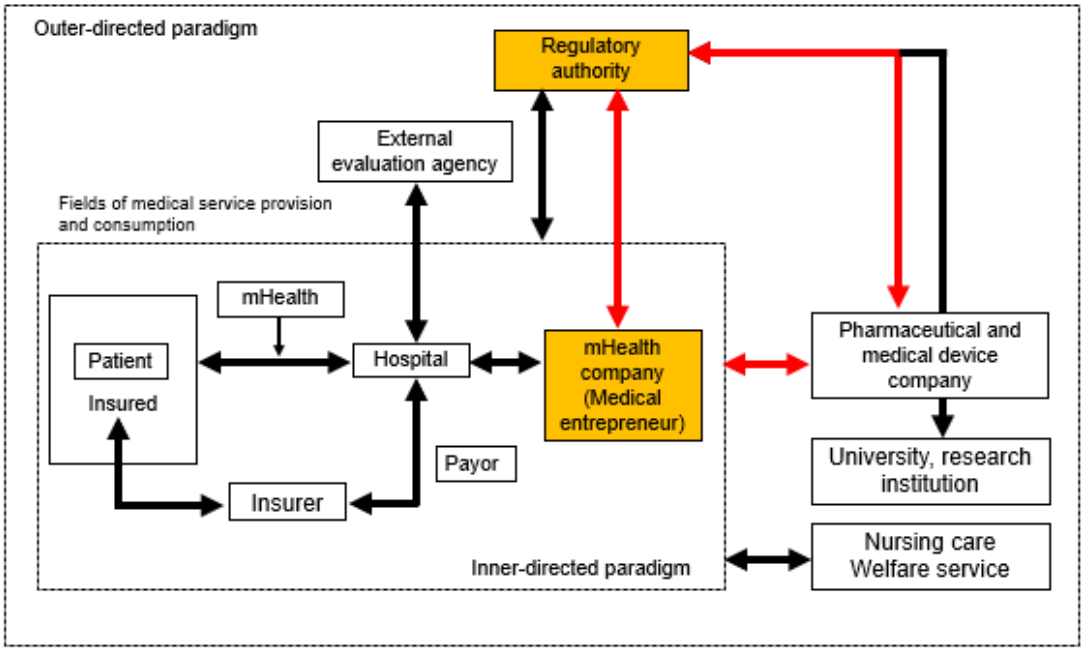

Figure 4-3. Potential paradigm innovators in mHealth

This figure shows paradigm innovators among stakeholders in mHealth industry.

Stakeholders with orange color are paradigm innovators in mHealth, and the relationships between them, symbolized by red arrows, are important.

4.6. Limitations

Although this study focused on the US as the largest mHealth market, observations in other regions are needed, considering that the mHealth market is growing worldwide, and comparisons between the characteristics and environments of each country should be made. In addition, the interviews carried out for this study were based on four experts only. For future studies, it would be advantageous to interview more people with diverse jobs including medical entrepreneurs, regulators, payers, and patients, especially to analyze changes in mental models. There is also a need to discuss the data collected by mHealth in the face of growing expectations for the use of data in healthcare.

4.7. Conclusion

The previous chapter examined and addressed the impact of mHealth on the medical industry from the paradigm innovation perspective. I focused on the relationship between regulation and mHealth innovation, and interviewed experts

in the mHealth sector to clarify the role of mHealth from inner-directed paradigm and out-directed paradigm. I revealed that ICT players enable the daily monitoring of patients for personalized care in inner-directed paradigm through mHealth. I identified the FDA and medical entrepreneurs as innovators driving innovative change in mHealth. It was confirmed that the FDA, as the regulator rule maker, had adopted a “interactive regulator” mindset in order to adapt to the digital health field, and that medical entrepreneurs and their companies had developed new markets by fusing innovative technologies with medical needs. This study presents important knowledge for considering future medical care scenarios with an understanding of the evolution of the marketplace brought about by the introduction of mHealth. Rather than a focus on technology as simply a new modality, it is instead the data created and outcomes achieved by mHealth that will define its value to the medical field and change the way itis evaluated. In each of these scenarios, the significance and meaning of mHealth should be defined is an important factor.

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CHAPTER 5. CONCLUSIONS

5.1. Summary and key findings

The purpose of this thesis is to explore how innovation affects the existing medical system, the process of mHealth innovation, and the relationship between the diffusion of innovation in advanced technology and regulations.

mHealth is an emerging field in healthcare. In 2011, US Secretary of Health and Human Services Kathleen Sebelius referred to mHealth as "the biggest technology breakthrough of our time" and maintained that its use would "address our greatest national challenge [1]". However, in spite of its significance, very few studies have addressed the dynamics of the mHealth industry from the perspective of innovation management. "What kind of technology?" "what kind of company leads the mHealth industry?" and "how can mHealth transform healthcare?" are all questions that need to be answered. For this reason, this thesis seeks to a provided deeper understanding of the role of mHealth and clarify the factors that cause changes in the healthcare industry. This study is based on the 4Ps innovation framework, which I adopted and adapted for the mHealth context as well as for advanced medical products and services.

First, I clarified the status of clinical trials within mHealth in Chapter 2 [2]. In this study, I observed the current status of clinical trials within mHealth. I confirmed that mHealth has shown double-digit growth in the number of clinical trials for a wide range of indications, including mental and behavioral disorders, and circulatory, endocrinal, nutritional, and metabolic diseases, in order to improve drug adherence. This was followed by an in-depth analysis of these clinical trials, showing that mHealth has two potential areas of application: product innovation in pharmaceutical R&D, as a form of therapy in itself, and process innovation, as a supportive tool for existing therapies. With regard to product innovation, therapies using mHealth are oriented towards cognitive behavioral therapy for mental conditions and addictions, implying that mHealth initiatives are expected to enhance patient engagement. With regard to process innovation, mHealth contributes towards improved medical adherence in a considerable number of clinical trials, whereas a dominant design has yet to appear. Then I observed that the current usage of mHealth in pharmaceutical clinical trials remains at a preliminary level of technology, such as bidirectional communication using text messaging or applications.

Second, in the third chapter titled "Innovation process of mHealth: An overview of FDA-approved mobile medical applications" I revealed the status of

mHealth initiatives approved by the FDA [3]. I examined the novelty of mHealth products approved by the FDA (N=189) from both technological and market perspectives. Through this, I found that new product developments in the existing medical market, that is, miniaturization and/or wireless technology, were in the majority (N=171), whereas innovative products for diversification or new market development remained in the minority (N=16 or 2, respectively). I found that current mHealth products differentiate themselves from preexisting medical equipment through miniaturization and wireless capabilities and that only 18 products were found to develop new markets based on cutting-edge technologies. In addition, forerunners in the mHealth market were found to be ICT companies and startups, not preexisting medical equipment manufacturers or pharmaceutical companies.

Moreover, I confirmed that products that develop new markets based on cutting-edge technologies were found to be developed by US-based companies established on or after 2001. These companies were found to provide added value to existing products by supplying preexisting players in the healthcare industry with mHealth as a supplementary asset. I also discussed the possibility that these companies may grow into platform leaders in the future market. I went on to examine how regulations may influence the growth of the mHealth market and referred to the possibility that, in mHealth, the clarification of policies and regulatory conditions may have encouraged enterprises to enter the market. Additionally, the number of mobile medical apps being cleared by the FDA in the United States has been increasing since 2010. I consider the sharp increase of approvals between 2013 and 2014 to be a turning point in the mHealth market, together with indirect contributions of regulations.

In the fourth chapter, I identified ICT players, interactive regulators, and medical entrepreneurs are as innovators driving innovative change in mHealth. I revealed that ICT players enable the daily monitoring of patients for personalized care as an inner-directed paradigm within mHealth. With regard to regulators, it is generally agreed today that technological innovation is conventionally seen as outpacing regulation. In contrast, the FDA, in the mHealth field, has taken on the role of an “interactive regulator” after adopting a forward-thinking mindset, allowing innovators to take advantage of new technologies through new regulations. In terms of medical entrepreneurs, it has become evident that some medical practitioners are now venturing into the mHealth market, starting their own mHealth companies, instead of joining existing pharmaceutical and medical device companies. A medical entrepreneur has the potential of being a data interpreter, filling the gap between patients, other medical doctors, and engineers. They do this by carefully using their

activities as doctors as insight and feeding this data into their mHealth companies and engineers, thereby, guaranteeing the accuracy of products based on their medical expertise.

As an overview, rule makers are interactive in driving innovation, and newcomers to healthcare value information through mHealth. Understanding the impact of mHealth on healthcare is important in predicting future changes in the healthcare industry.

Observations on the current status of clinical trials and related approvals show that their use within mHealth is limited and that technology adoption remains at a primitive level using general-purpose products and services only. Nonetheless, the entry of companies into the market is budding. From a technical perspective, mHealth is synonymous with incremental innovation. Since medical health technology companies do not have continuity within the existing medical device market, doctors are establishing companies that develop and open up the market for mHealth, a highly novel phenomenon, and the FDA's newly adopted role in supporting market formation is helping the emergence and sustainability of these doctor-led companies. mHealth has pioneered ICT in healthcare based on not only technological advances, the diffusion of devices, and communication technologies, but also on the emergence of new companies and regulatory changes.

5.2. Implications

5.2.1. Theoretical implications

First, I designed an appropriate framework to analyze mHealth's position in the healthcare industry based on the 4Ps of innovation space by Tidd and Bessant [4]. This framework helps to identify areas in healthcare that are relatively unexplored and may offer significant innovation opportunities for mHealth, areas where the industry currently has innovation and those it might explore in the future, and the unique features of mHealth.

The medical landscape has undergone large and unprecedented changes thanks to the latest technologies. A series of analyses on the changes in products, processes, positions, and paradigms associated with the advent of mHealth provided insights that could not be obtained by simply observing trends in existing pharmaceutical and medical device companies (in terms of the background of and response to these changes in healthcare). This framework helps to understand the impact of mHealth on healthcare and presents important insight into future medical scenarios.

Second, I found “interactive regulators” such as the FDA to support innovation in mHealth. Technological innovation is conventionally seen as outpacing regulation and a new framework to change “Innovation first/regulation after” to “co-development of regulatory arena and novel technology” is needed [5][6]. From examining the findings, the FDA is adopting a mind-set that promotes innovation as an “interactive regulator” in the field of mHealth. The US government enacted core federal law for healthcare ICT in 1996. The sharp increase of approvals between 2013 and 2014 became a turning point in the mHealth market, together with indirect contributions of regulations. Through pre-cert programs, the FDA captured a trend of ICT and streamlined the regulatory review process to help encourage digital health innovation. It is through this co-developing regulatory framework with small start-ups, large companies, and regulators that enables innovators’ disruptive success.

Third, I revealed that the current mHealth industry is being shaped, not by incumbents, but by new entrants or start-ups that bring expertise in the field of ICT. I found products that develop new markets based on cutting-edge technologies were found to be developed by US-based companies established on or after 2001. These companies were found to provide added value to existing products by supplying preexisting players in the healthcare industry with mHealth products as supplementary assets. I discussed the possibility that they may grow into platform leaders in future markets.

5.2.2. Practical implications

Information technology has played a vital role in the innovation of healthcare systems. It has been eight years since mHealth was called “the biggest technology breakthrough.” Today, mHealth is recognized as a new modality in medical care. An mHealth technology provider can provide complementary assets [7] to pharmaceutical companies, thereby enabling the latter to increase the value of their existing products and deliver better outcomes. In the examples of Otsuka Pharmaceutical, which developed digital medicine with Proteus in 2017 [8], and Roche, which acquired MySugr in 2017 [9], it is evident that these pharmaceutical companies understand that collaborating with a technology developer is necessary to acquire complementary assets as a strategy for success. At the time that I conducted the empirical study mHealth solutions with clinical trial.gov, there were few pharmaceutical companies using for clinical trials. However, today, more pharmaceutical companies are adopting mHealth for their clinical trials. For example, Sanofi collaborated with Science 37 in March 2017 to conduct virtual

clinical trials using mHealth [10]. Science 37 is a company that aims to leverage the power of mHealth and telemedicine to help conduct patient-centered trials, thereby making time-consuming, expensive clinical trials more efficient and faster through innovative ways [11]. In March 2018, Novartis entered into a partnership with the same company [12]. Takeda also entered into a strategic joint research agreement with Cambridge Cognition to explore biomarkers in the central disease field using mHealth in February 2017 [13].

Pharmaceutical R&D provides a source of knowledge and serves as a platform of innovation for mHealth products and services developers. However, in the context of platform leadership [14], there is a possibility of a technology developer evolving into a platform leader and a pharmaceutical company assuming the role of a complementor.

At the same time, quintessential ICT platform companies such as Google, Amazon.com, Facebook, and Apple have been rapidly increasing their presence in healthcare in recent years. The number of healthcare-related patents filed by these four companies from 2009 to 2017 has been led by Microsoft, with 140 patents, followed by Apple and Google with 40 patents [15]. Microsoft holds patents for collecting and analyzing electronic medical record data, then sending automatic alerts regarding medication interactions, in addition to patents for predicting disease risks from genomic information [15]. Apple has published a Research Kit that has increased the usage of iPhones in research [16], while Google is trying to predict disease risks from unstructured healthcare big data [17]. Furthermore, Amazon.com announced in June 2018 that it would acquire the online pharmaceutical seller PillPack [18]. PillPack was founded in the U.S. in 2013. It is a prescription drug delivery service that also provides usage instructions and has a growing number of customers, particularly within the elderly demographic, with over 23 million U.S. customers. After Amazon's acquisition of PillPack and the launch of its healthcare JV with Berkshire Hathaway and JP Morgan, some expect Amazon will move deeper into the world of pharmaceuticals in the future [19].

With societal changes and technological changes in medical care, companies entering the field are also changing, and the pace of change is accelerating. For example, Google, Amazon.com, Facebook, and Apple now have wearable devices, smart speakers, and similar products, differing significantly from existing players in the healthcare field given their potential to improve the user experience. Companies newly entering the healthcare field through the progress of these kinds of ICT and the emergence of new platforms are building complementary relationships with various players along the medical value chain.

I consider the possibility that they will eventually gain platform leadership in promoting the evolution of the entire value chain with data. In the healthcare field, the utilization of data, especially personal data, is promising [20]. The use of data in healthcare has the potential to improve decision-making and address inefficiencies in the healthcare ecosystem. IoT can enable continuous monitoring, irrespective of the presence of healthcare professionals, and even alert them when necessary. Diagnosis, monitoring, and treatment can occur regardless of patient location, enabled by IoT. As the amount of data available through wearable devices and sensor technology increases, pharmaceutical and medical device companies may own drugs and pharmaceutical products, but other companies may own the surrounding information. It is expected that the time will come when there will be a difference between the owner of the object and the value of the information.

5.3. Limitations and Future Perspectives

Because this study focused on the US as the biggest mHealth market, it is necessary to observe in other regions, considering that the mHealth market is growing worldwide, and comparisons between the characteristics and environments of each country should be drawn. Moreover, further analysis is needed to improve treatment outcomes and cost-effectiveness, which are adopted by payers after regulatory approval and actually achieved by mHealth in the clinical setting.

There is also a need to discuss the data collected through mHealth in the face of growing expectations about the use of data in healthcare. mHealth companies are able to capture data between patients and healthcare professionals that was previously unavailable to major pharmaceutical and medical device manufacturers. Because of mHealth, data can now be digitized, stored, and then stratified and divided into subgroups, potentially leading to precision medicine. Data captured without time and space constraints, and generated by combining existing medical and mHealth data, will create new value. In the future, I would like to deepen our research on mHealth and conduct research on the utilization and value of data in healthcare.

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APPENDICES

Supplemental table 1. Description of the three selected applicants in the new product development quadrant

Company		Established	Country	Regulation medical Speciality	Regulation Descreption	Device Name	Number	Year of FDA Sent Letter	Class
LifeWatch Technologies Ltd	Card Guard Scientific Survival	1986	USA	Cardiovascular	Telephone electrocardiograph transmitter and receiver	TM05 PERSONAL MEDICAL PHONE CENTER	2	2003	Ⅱ
						CG-6108 ARRHYTHMIA ECG EVENT RECORDER		2006	
					Arrhythmia detector and alarm (including ST-segment measurement and alarm).	CG-6108 CONTINUOUS ECG MONITOR AND ARRHYTHMIA DETECTOR	5	2007	
						CG-6108 ACT-3L CONTINUOUS ECG MONITOR & ARRHYTHMIA DETECTOR		2008	
						CG-6108 ACT-i L Continuous EGG Monitor and Arrhythmia Detector		2010	
						MODIFICATION TO: CG-6108 ACT-3L CONTINUOUS ECG MONITOR AND ARRHYTHMIA DETECTOR, MODEL FG-00084			
						CG-6108 ACT-3L Continuous EGG Monitor and Arrhythmia Detector		2011	
	LifeWatch Technologies Ltd		Israel	Cardiovascular	Arrhythmia detector and alarm (including ST-segment measurement and alarm).	Vital Signs Patch System (In Short Vsp)	5	2014	
						CG-6108 ACT-3L Continuous ECG Monitor and Arrhythmia Detector		2015	
						ECG Mini System Continuous ECG Monitor And Arrhythmia Detector		2016	
						Vital Signs Patch System			
AirStrip Technologies		2004	USA	Obstetrics/Gynecology	Perinatal monitoring system and accessories	AirStrip OB	3	2005	Ⅱ
						AirStrip OB		2009	
						AirStrip OB			
				Cardiovascular	Cardiac monitor (including cardiotachometer and rate alarm).	AIRSTRIP REMOTE PATIENT MONITORING (RPM) REMOTE DATA VIEWING SOFTWARE, VERSION 3.1	6	2010	
						AIRSTRIP REMOTE PATIENT MONITORING (RPM)		2011	
						Airstrip Remote Patient Monitor			
						AIRSTRIP REMOTE PATIENT MONITORING (RPM) REMOTE DATA VIEWING		2012	
						Airstrip Remote Patient Monitoring		2014	
						AIRSTRIP REMOTE PATIENT MONITORING			
				Obstetrics/Gynecology	Home uterine activity monitor	Sense4Baby	1	2015	
Andon Health Co. Ltd		1985	China	Cardiovascular	Noninvasive blood pressure measurement system.	KD-930 Fully Automatic Electronic Blood Pressure Monitor	6	2011	Ⅱ
						KD-936 Fully Automatic Wireless Blood Pressure Monitor		2012	
						KD-7964 Fully Automatic Electronic Blood Pressure Monitor			
						KD-972 blood pressure monitor		2015	
						Fully Automatic Arm Cuff Electronic Blood Pressure Dock BP3			
						Fully Automatic Electronic Blood Pressure Monitor		2016	
					Oximeter	IHEALTH FINGERTIP PULSE OXIMETER	1	2013	
				Clinical Chemistry	Glucose test system	IHEALTH ALIGN MINI GLUCO-MONITORING SYSTEM	2	2014	
						IHealth Align Gluco-Monitoring System, IHealth BG5 Wireless Smart Gluco-Monitoring System, IHealth BG5L Wireless Smart Gluco-Monitoring System		2015	

Note: three applicants in the new product development quadrant are listed in the descending order of product approval number with company's profiles and details of approved products.

Supplemental table 2. Description of selected three applicants for novel products

Company	Established	Country	Regulation medical Speciality	Regulation Description	Device Name	Number	Year of FDA sent letter	Class
Proteus Digital Health	2001	US	Cardiovascular	Telephone electrocardiograph transmitter and receiver	Raisin Personal Monitor	3	2009	Ⅱ
			General Hospital	Ingestible event marker	Proteus Patch, Proteus Ingestible Sensor		2013	Ⅱ
			General Hospital	Ingestible event marker	Proteus Digital Health Feedback Device		2015	Ⅱ
Welldoc	2005	US	-	General Hospital	DIABETESMANAGER SYSTEM, DIABETESMANAGER RX SYSTEM MODEL VERSION 1.1	3	2010	Ⅱ
			General Hospital	Infusion pump	WellDoc DiabetesManager System and DiabetesManager-Rx System		2011	Ⅱ
			General Hospital	Infusion pump	WellDoc DiabetesManager System and Diabetes Manager -Rx System		2012	Ⅱ
Reciprocal Labs corporation	2007	US	Anesthesiology	Nebulizer	Asthmapolis System	6	2012	Ⅱ
					PROPELLER SYSTEM - MODEL 2		2014	Ⅱ
					Propeller System 2014-R		2014	Ⅱ
					Propeller System		2014	Ⅱ
					Propeller Model 2014-D Sensor		2014	Ⅱ
					Propeller Sensor Model 2014-R		2015	Ⅱ
					Propeller System		2015	Ⅱ

Note: three applicants in the novel product development quadrant are listed in the descending order of product approval number with company's profiles and details of approved products.

Supplemental table 3. Biography of interviewee

- George Savage, MD: Co-Founder, Chief Medical Officer, Proteus Digital Health

Dr. George Savage is Chief Medical Officer and Co-Founder of Proteus Digital Health, and formerly the company's vice president of research and development. He sees Digital Medicine as an invaluable collaboration platform for patient and physician, integrating information about a patient's response to therapy directly into everyday healthcare. He is focused on developing the clinical and economic evidence needed to secure global regulatory approvals and spur widespread adoption of Proteus's ingestible sensor platform. Dr. Savage has a successful 27-year track record of starting and developing technology-based healthcare companies in Silicon Valley, having started ten companies since 1989 as entrepreneur or founding investor, including FemRx (acquired by Johnson and Johnson), CardioRhythm (acquired by Medtronic) and QRx Pharmaceuticals (ASX IPO).Dr. Savage holds a B.S. in biomedical engineering from Boston University, where he graduated magna cum laude and Tau Beta Pi, an M.D. from Tufts University School of Medicine and an M.B.A. from Stanford University Graduate School of Business. Dr. Savage serves on the boards of Menlo Healthcare Ministry and Silent Cal Productions, the California Life Sciences Association, the Boston University College of Engineering advisory council, and in 2016 was elected a Fellow of the American Institute for Medical and Biological Engineering.

- Megan Coder, PharmD, MBA: Executive Director, Digital Therapeutics Alliance

Megan Coder, PharmD, MBA, is Executive Director of the Digital Therapeutics Alliance. DTA's mission is to broaden the understanding, adoption, and integration of clinically-evaluated digital therapeutics into mainstream healthcare through education, advocacy, and research. With more than a decade of experience in the healthcare industry, Megan's expertise extends from strategic growth and partnership development within the digital health sector, to the direct delivery of patient care. Prior to joining DTA, Megan worked with Voluntis, Iodine, the Pharmaceutical Care Management Association, and the Pharmacy Technician Certification Board. Megan graduated from the University of Wisconsin—Madison School of Pharmacy and completed an Executive Residency in Association Management & Leadership with the American Pharmacists Association.

- Arthur Hermann: Principal Technology Consultant, Strategy Planning, Kaiser Permanente

Arthur works for Kaiser Permanente, an organization that provides all insurance, hospital, and healthcare services to over 12 million members across the United States. He has over 18 years of experience in Health Information Technology, including Enterprise Architecture and developing the Service Oriented Architecture (SOA)/APIs, which are used at Kaiser Permanente to move millions of messages per week. Most recently, Arthur has been working on Precision Medicine strategies, data management, and technology. He is a voting member of the HL7 Genomic Working Group. Arthur is a Fellow to the World Economic Forum's San Francisco Center for the 4th Industrial Revolution, with a focus on Precision Medicine and health data. Arthur graduated from the Golden Gate University, Information Systems

- Emilio Merlo Pich, MD, Ph. D: Executive Medical Director in Clinical Science, Neurology, Takeda Pharmaceutical Company.

Emilio Merlo Pich, MD, Ph. D is a neurologist and neurobiologist with expertise in Pharma R&D and interest in developing new treatments for nervous system disorders. In the last 20 years he has been engaged in various roles related to biomarkers and early clinical development in the Neuroscience Therapeutic Area, at first in GlaxoSmithKline and its legacy company Glaxo-Wellcome, where he led the Experimental Medicine and Molecular Medicine functions, and more recently, in F. Hoffman- La Roche, Basel Switzerland, where he was in charge of CNS Biomarkers and Imaging. He graduated in Bologna, Italy and was in academia at the University of Modena, at Karolinska Institute of Stockholm, Mario Negri, Milan, and at the Scripps Research Institute, La Jolla. Emilio Merlo Pich is co-author of more than 200 publications. He received several awards throughout his career, and he is Fellow of the American College of Neuropsychopharmacology (ACNP).

Supplemental table 4. Questioner: questioner for interview

1. Background information ・Biography ・Affiliation and role in the company
2.Question about mHealth ・ What do you think about mHealth innovation on your business? ・ Which players is the most key players on mHealth? ➢ e.g. Doctor, hospital, tech company, medical device company, pharmaceutical company, payor …etc ・ Do you think "medical entrepreneur" is key players in mHealth? ・ Why did you start own your company as physician? ・ ・ What do you think about FDA on mHealth? ・ Which regulation/guide line are related to your business?? ・ Do you think regulation push or support to innovation on mHealth or obstacle? ・ Who do you think will lead mHealth industry? ・ What do you think about obstacle/opportunity to progress on mHealth?
3.Free comments

Supplemental table 4. Question and answer of interview
Interview with Dr. Savage.

1. What do you think about mobile health innovation on your business?

Dr. Savage: Mobile health is the core of what we are doing at Proteus At Proteus we're leveraging the mobile computer that everyone carries with them, called the smart phone, to try to dramatically improve the real-world effectiveness of pharmaceutical therapy. Few people understand that everywhere in the world adherence to medication averages less than fifty percent, and physicians also don't know the details of how patients may be taking their drugs inappropriately, and therefore don't know whether or not to revise the diagnosis or how to advice the patient on how to do a better job. And it's an information problem and we believe, and have demonstrated, that by building objective feedback and measurement into drug therapy we can help patients take their drugs better and also help physicians make better decisions.

2. Which players is the most key player in mobile health in US for example doctor, hospital, tech company?

Dr. Savage: It may be considered self-serving but we would say that the best the biggest player in mobile health right now in the Unites States is Otsuka, Japanese company, Otsuka Pharmaceutical because they are the first company in the world to have gained FDA approval on a fully digital drug and that's a drug with a sensor built in to it to signal exactly when it's been taken and this is for a product called Abilify Mycite in America and it is directed to treat schizophrenia and bipolar disease and serious mental illness. And of course mental illness is a very significant problem around the world, and it requires treatment the good news is appropriate treatment can really help patients lead more normal lives and the sad thing is that if someone forgets to take their medicine for very long, they often… their disease will progress and they'll lose the insight that they need help and they can deteriorate. And so by building feedback into Abilify Mycite, Otsuka has committed to trying to address this by offering this built in feedback for psychiatrist and their patients and they've introduced the product in the United States and have applied for approval in Europe and are talking to regulators in Japan as well, so I think they're a very good company. I should mention the technology they built in is Proteus's, of course so I'm self-interested in that respect, but I think this is a very big a big deal.
There are many who are using a digital medicines in the field of organ

transplantation there would be a doctor Dev Desai at Dallas children's hospital in Texas and in cancer therapy there's a doctor Edward Greeno at Fairview health system University of Minnesota. There are… a doctor Mark Skalski at Johns Hopkins University in the area of Hepatitis C treatment. Those are three. Furthermore, there are many digital innovation officers, chief innovation officer or a digital health officer. Many different health systems are trying to explore how software and the availability of mobile phones can be used to improve the health of their patients and the population that they treat and also how it can be used to help engage with the community and encourage better health and streamline their operations.

3. Who has a right to choose the new technology this chief digital officer or medical doctor in clinical practice side?

Dr. Savage: It's very complex now, the US health system is in great state of flux. Over the last decade there has been a lot of consolidation as large health systems buy up formally independent medical practices, and also by other hospitals, and even many firms are trying to expand into different lines of business like going financially at risk so they behave a bit like an insurance company or provider or rather a payer, to pharmacy benefit management…there's been a lot of crossing of boundaries and so this has meant that depending on the type of digital health solution that's being offered, it's complex to sort out exactly how to get it adopted and prescribed, so and it also depend on the ambition of the app. Is an application merely trying to help a patient to sleep better or to identify how to be more active during the day…that is pretty straight forward for the patient to be in charge of and to simply download an app on your smart phone. But if you're trying to integrate with the health systems electronic medical record and to change how care is delivered that's a more much complicated scenario so the innovation officers typically highlight companies and solutions in sort of labs or innovation labs inside of a health system mainly to introduce doctors and other executives in the health system to what's possible and what they may do and then there may be contracts that are executed by the business leadership of a health system and then you have the issue of whatever they've contracted for being implemented. At the end of the day, a physician typically prescribes these sorts of tools, if indeed they are prescription products, but in order to be able to do that there's a lot of other steps involved so this has made adoption of many digital health solutions complicated and take longer than some might have predicted.

4. How about medical device company so in my research some big medical device company enter digital health but it's not big trend so what do you think about the trend of medical device company in mobile health?

Dr. Savage: First of all It depends on the definitions because many companies are active in digital health there are hundreds of thousands of software applications that are health related and so if you think of digital health meaning the use of smart phones and computer technology for health-related purposes, that's very large. And some software if it's performing a regulated function, can be considered software as a medical device, so there are some apps, the minority of course, that require regulatory review and those companies would be medical device companies by themselves. On the other hand, you have traditional medical device companies that make things like imaging devices and pacemakers and you know things that we all would recognize as a medical device, and many of them are also embracing digital health or aspects of it, so if you think of patients that treat diabetes, many of them now have glucose sensors that report results not on a special medical device but on the patient's mobile phone and they allow the patient to track and trend their blood sugar and sometimes enter information about their diet and other things to help them manage their insulin administration and through the measurement of the product. So, these medical device companies are not primarily digital health companies but in their traditional device business they've embraced the consumer good which is the smart phone and they need to put the consumer, the individual patient, at the center of the experience you know through an app on the phone, and so that's sort of a hybrid model. And so there's a big spectrum between a fitness app, say, in a company that does something like that, versus a company that has a medical device application to try to, say, help treat a patient with depression and a medical device company that makes say a glucose monitor or an insulin pump or both that has an app for the patient on their phone.

5. What do you think about the trend of medical doctor entrepreneurship in mobile health?

Dr. Savage: It's a fair point—there are many physicians and other people with experience in the medical profession, either because of their scientific background or their business background, who become entrepreneurs and medical doctors are moving into the medical, the mobile app space. I think it's fair to say that the IT (Information Technology) side of the medical arena has drawn a lot of attention and a lot of new entrance because it's a new field which means there are not established

incumbents that dominate, and whenever there's something that's brand new there's a lot of excitement and innovation and the opportunity to grow something, you know from the beginning without a major company standing in your way and so that's attracted a lot of excitement and interest. I think it's fair also to say though that many of the digital companies, digital health companies have not grown as quickly or received the adoption of their products that they would have expected, and so it's been relatively more challenging to generate significant revenues and significant company growth in most digital health companies and I think that is related to the complexity of the US health system as it's evolved over the last ten years which I explained earlier.

6. Why do you think to start up in your company in mobile health field?

Dr. Savage: We were struck by the fact that all around the world no matter what country you're in or what diagnosis a patient has, patients, only about one in two, one half of patients benefit from drug therapy they either don't know how to take their drugs correctly or the doctor has them on the wrong dose of a drug or the wrong drug, and the trouble is since the physician can't tell if the patient is taking the drug right or not the doctor can't make better decisions and the patient has no measurement, no feedback, no behavioral cues, nothing to help them learn what a good job looks like versus a bad job. And if we think about it, the way people learn how to get better at anything be it sports, or being at work, or being a student at school, is through feedback—you take a quiz and your teacher will mark where you've got the wrong answer and perhaps help you understand what you need to work on so that you will learn something that you haven't quite sorted out. No one would really advocate just giving a textbook to a child and say come back in a few months and there'll be a final exam, because you wouldn't expect them to learn that well. When you learn to drive you have an instructor who explains what you're doing wrong, when you are at business you have an advisor or a manager who will talk to you, but our patients don't have any of that and so we thought that this is the very biggest public health problem in the world. If the pharma company discovers a brand new molecule that can do some wonderful thing for the treatment of a disease, but if that drug has to be taken chronically by patients then most patients won't benefit from it and all the money spent on it would be wasted, and so we believe that this measurement and feedback problem is mainly an information problem so therefore the mobile phone and digital technology could be part of that solution and we thought that would be a very exciting thing to work on which is in addition to pharmacology

and chemistry, introduce the concept of software, silicon, and physics into a drug so that you leverage this mobile connectivity and build that into drug therapy and get better results.

7. What are the hardest things to start up your company?

Dr. Savage: Starting and developing and I would have to say that in terms of where we are now commercialization is the main challenge, again because of the complexity of the US health system we already described. Earlier we had issues educating regulators and getting regulatory approvals, but we've surmounted those and we're left with commercial. When you're first starting up, of course the main challenge is securing capital and is raising finance, raising money that you need to start the organization and sorting out a plan where you can very efficiently use the money that you've earned from, you're given by investors to reduce the risk of further progress to the enterprise so that as the risk is reduced the value of your company is higher and therefore you can feel confident that as you raise more capital you can do it in a way that is more efficient, in other words not diluted to earlier investors where they feel like you're making progress and their money is earning a return. So, that's always a challenge it's a good one though because that imposes discipline on the management of the company, the founders and then the team, and that discipline forces you to be rigorous and to work hard and to make appropriate choices and so it's not really a negative, but it is a challenge.

8. Is the environment to start a company good for you in US?

Dr. Savage: Silicon valley is very good. That is the you know one reason why the San Francisco area here in California is a frequent destination for people from all over the world because despite it being a very expensive place to live in terms of real estate costs and the taxes and other costs, the benefits of the ecosystem here are very high and so we have a culture that is very acquainted with entrepreneurs starting companies and doing well and therefore you have a workforce that is very accustomed to leaving, say, an established company to join a brand new one and they don't worry about the risk that they might not be able to be hired again if the company failed, because everyone understands companies fail sometimes and that's okay there are investors, many investors who similarly invest in risky startup companies because some do extremely well and some don't and they're again happy with that sort of calculation and the same goes to the landlords who rent you the buildings and on and on that goes. So, there's a very strong culture here where all

parties understand that new innovative companies can yield tremendous success but don't guarantee tremendous success by any means and so it's okay to fail provided that of course you're striving with all your ability for success and of course many of the companies do succeed.

9. What do you think about FDA on mobile health?

Dr. Savage: FDA on the medical device side the Center for Devices in Radiological (CDRH) they have, under doctor Gottlieb's leadership at FDA, work to modernize the approach to approving software so Bakul Patel runs the digital health center of excellence at FDA and he's done a very good job at bringing software regulation into a more modern context where regulation is lighter and can move at the speed required to have up to date products that would run on a patient's mobile phone so very positive results there. On the drug side of FDA, when you're thinking of what are called drug device combination products, there the agencies still have some work to do because the drug regulators treat software very differently even the identical software that's treated in a very light way over on the device side, if it's associated at all with a drug, it's treated in a very stringent and slow manner on the drug side and so, FDA still has some issues to work through in terms of collaborating between centers of the drug regulators or in the center for drug evaluation and research which is a different division of the agency, different center than the device regulators and so, the main need going forward is for regulators to have one voice when it comes to software and digital regulation without regard to whether it's part of a drug or device.

10. Which specific regulation or guideline related to your business?

Dr. Savage: We've done many different approaches when we first introduced our ingestible sensor technology there was no prior category at FDA for this device, it was too innovative. And so that was…but it's very low risk so a premarket approval was not appropriate on the device side so what FDA did was they created a new class two category for the device doing what's called the De Novo approval that's a approval of a new class to device category so that was very innovative and then we've had subsequent devices cleared by what's called 510(k) a premarket notification referring to our De Novo approval. Then on the drug side our partner Otsuka has obtained a new drug application approval an NDA approval under what's called 505 (b)(2). It's a type of NDA pathway for the combination of a drug with the ingestible sensor where the two are built together in the factory, in Tokushima actually, and then shipped in to the Unites States.505 is the NDA portion of FDA and a 505 I think

it's (b)(1) or is it 505 (a) I forget anyway…that's where the various type of drug approvals are listed in the regulation. One is for a new molecular entity, a brand-new drug. One is for a drug where you've changed something, and in this case that would be Abilify which has already been on the market in the past, but having the sensor added to it made it a 505 (b)(2). Then they have an ANDA, an abbreviated new drug application which is for generic drugs and that's I think 505 (j) or something like that.

11. Do you think regulation or guideline of FDA push to innovation of mobile health or not?

Dr. Savage: Yes, positive to supportive. I'd say it's been challenging. FDA has been supportive of what we're doing. I think some of the response on the drug side for the drug device combination approvals has taken longer than we would expect, and I think part of that is because drug regulators tend to view the world a certain way based on how drugs work and sometimes don't understand that that's not necessarily appropriate for regulating software. The fundamentals of regulating the drug come about from the fact that drugs are meant to interact with the human body and we really don't know for sure how human beings work. We have good models and we understand incompletely but a drug regulator often has to be very careful because any change could have change everything, and so they have to be very cautious in that way. When you're writing software and things of that nature on the information worlds, typically these are things that people did design, we do know all about it and so you can operate much more quickly and indeed being too slow is often a risk because if you wait too long you don't make the progress that you would make if you could iterate, that is continue to evolve your software more quickly.

12. What is obstacle or challenge to progress on mobile health?

Dr. Savage: The obstacles to us primarily, right, is the existing way of doing business, you know, The Healthcare system is very complicated all around the world and it's very big and very important and to move to a new business model we believe could unlock tremendous value for the patient and for businesses that are helping those patients and for payers who are paying for the care of those patients because we could yield better outcomes for patients without spending more money by making sure that the drugs that are already being prescribed work much better. The issue is that's very hard work because you have to change medical practice and many companies in our business right now find it easier just to raise prices and as you

know price increases in pharmaceuticals, particularly in the US, is a very big topic right now one of the very few that unites people across the political spectrum from people who like president Trump to people who don't like president Trump, most politicians agree that drug prices are too high and keep going up too quickly and so but it is an obstacle because as long as drug companies feel that they can raise prices to meet their objectives it's very hard to put in the work necessary to transform how Healthcare is delivered to yield more value for the payers and the patients. So I would say the commercial barriers are the biggest thing to work through. Now the good news is that there is a lot of consensus politically and economically that drug prices are going up too high Healthcare cost too much and so something must be done so that's the countervailing force but the obstacle right now is just the way things have being going for now many years it's just prices go up every year, and well, you know why do anything very different.

Interview with Ms. Megan.

1. What do you think about mobile health innovation on your business?

Ms. Megan : I think m-health has an important role to play in supporting digital therapeutics and digital therapeutics may also support m-health—I haven't thought of it in that direction as much but I would at this point put a line down the middle saying these are making medical claims that would need to be regulated as a medical device, whereas these are medical devices, possibly, but they don't have the same level of risk, hence they don't have the same level of regulation. ELEKTRA LABS is starting to look at all of the possible wearables that exist that could be used for a clinical trial or that could be used within a digital therapeutic. They're starting to put together a library of all of the m-health products that could be used either to support a drug trial, or to support a digital therapeutic, as an example. There are different groups that are out there that are looking at "how do they ensure that the product is what it says it is," "that it does what it says it's going to do and that it's going to be reliable in the situation where it would be combined with another product." If we are doing a digital therapeutic we need to make a medical claim but then we also need to do clinical validation, and we've said that we have to have at least one full randomized control trial for every single product—and that is a high barrier like that we have to have a special set of knowledge, and then we have to undergo clearance by the FDA most likely, unless we are in this direct-to-consumer category. There's a few in that space like OMADA and Big Health, they don't have to go under FDA but they still need to do full scale randomized control trials, so it's a little bit more difficult in the digital therapeutics space because we have to have the knowledge of a clinicals study background, we have to have the medical device background, we have to have the FDAs device side background.

2. Which players is the most key player in mobile health in US for example doctor, hospital, tech company?

Ms. Megan: The regulatory agencies and the payers is key players to make that determination of risk and coverage right now. mHealth and digital therapeutics are slightly different. I think an mHealth product can go straight to a patient for some of the products they're creating. Digital therapeutics have to go through a payer or an employer sponsored program. At this point that digital therapeutics industry is so new that as they are creating the new definitions of this new category of medicine, going through they have to have been regulated. Having regulatory agencies—be it the PMDA, be it Health Canada, NHS, FDA—they need to be involved in determining the level of risk that those products bring, and hence, the level of

regulation. The other group that's important at this phase of the industry are payers; unless these are covered by payers the industry won't take off. It won't happen because even if they have a direct-to-consumer digital therapeutic it's still being covered by an employer or payer. Their even direct-to-consumer digital therapeutics do not have a direct-to-consumer pay model so that's a little different there. If I develop a digital therapeutic product it can be a direct-to-consumer, it can be an OTC or an Rx. The way that the FDA has gone, so far depending on the level of risk. If we are only addressing the condition but we not making a full medical claim such as "I'm going to treat your insomnia", FDA does not regulate these products, so this is a direct-to-consumer model. But even these products, even though they go straight to consumer, they are covered by employers and payers and you have to have an activation code to get into the product so we cannot just download a digital therapeutic and just start using it. If we're making the claim to actually treat a disease or disorder, then you're either an over-the-counter product or an Rx only product. These are the ones that have to have regulation. Once we get there then we will have to focus on the health systems and then we'll have to focus on the physicians and the health care providers and then the patients. I think they can go to the patients first or the consumers and then work their way up to the providers and then the payers whereas digital therapeutics we have to start at the regulatory and work down, which is different".

3. What do you think about the trend of medical doctor entrepreneurship in mobile health?

Ms. Megan: I think that the mHealth industry is still so small that there is no large sample size to pull from the medical entrepreneur in mHealth. One of the individuals, who's a co-founder of Rhythms is medical doctor. They're using a sensor plus a digital therapeutic plus music to help stroke patients rehabilitate their walking after a stroke incident. He worked in that space as a clinician, but I would like to say that this is just one example.

4. What do you think about FDA on mobile health?

Ms. Megan: FDA eager to support and also develop the digital therapeutic space, and they're doing a very good job with trying to figure this out. This all goes back to the International Medical Device Regulators Forum (IMDRF). They are going to be important. They put out a classification called SaMD, "Software as a medical device". IMDRF is a group of thirteen or so regulatory bodies that came together to create

the “software as a medical device” criteria and framework. Japan is one of those countries. IMDRF put out some ideas around the clinical guidelines we must have, or the clinical validation, in addition to some of the quality. FDA has done a very good job of implementing the Clinical Medical Device criteria as written into their process. They don’t have a specific focus yet though on digital therapeutics at this point. They consider all SaMD as all SaMD and they haven’t really broken it down into specific categories yet. FDA is also doing work with “The Software Precertification (Pre-Cert) Pilot Program”. Pre-Cert pilot program, as outlined in the FDA's Digital Health Innovation Action Plan, will help inform the development of a future regulatory model that will provide more streamlined and efficient regulatory oversight of software-based medical devices developed by manufacturers who have demonstrated a robust culture of quality and organizational excellence, and who are committed to monitoring real-world performance of their products once they reach the U.S. market. This proposed approach aims to look first at the software developer or digital health technology developer, rather than primarily at the product, which is what we currently do for traditional medical devices. Because software products can be adapted to respond to glitches, adverse events, and other safety concerns quickly, the FDA is working to establish a regulatory framework that is equally responsive when issues arise to help ensure consumers continue to have access to safe and effective products. In the Pre-Cert program, the FDA is proposing that software products from pre-certified companies would continue to meet the same safety and effectiveness standard that the agency expects for products that have followed the traditional path to market.

If we are going to use your product alongside of a medication or even in place of a medication, we just need it anyways for the safety and effectiveness. There is strong value in starting to identify a strong framework where we can as an industry point to, to say “if you’re going to be making these claims you have to be regulated, here are the regulations you have to adhere to.” If that is a baseline assumption, that enables companies to have even more innovation. Having a framework that everyone can appreciate and understand and vault into based upon the level of risk and the level of claim we are making does help innovation and it encourages more people to take more risk in terms of “I’m going to try to eventually make the claim to treat this disorder.” We may not be able to prove that in a single trial, then we may just have to say, “I want to manage this disorder” and eventually by the time we collect more data we could have different product iterations or learn more lessons to actually make to move that weight toward treatment. Framework is a necessary for patient’s safety, but then it also gives people something to look to and investors are more

appreciative of…they know now what the value is and that there is a pathway, as opposed to "we're just going to make claims and hope for the best."
In digital therapeutics a regulation from the FDA is actually a baseline minimum. It not the highest goal digital therapeutics company are trying to achieve. Its setting the baseline standard of "if you want to have an entry to market this is the minimum level you have to have." Therefore, they as an alliance have actually started to put in best practices and principles that actually step above what the FDA has been saying. An industry important for us to have credibility beyond just "We're safe." However, how about what's the ongoing evidence, how do you show that the product has integrity throughout its entire life cycle as opposed to this one-time clearance. There is no certification body, per se, for these products, so lot of it has come to the industry's self-guiding in terms of "here's what we believe that we all need to do in order to ensure the quality."
FDA, it only looks at the safety and effectiveness of a product. They don't necessarily look at the quality of a product. Based in this situation, DTA are working with the US pharmacopeia and they have a counterpart here in Japan called the Japan pharmacopeia—to see if there is a way to create quality standards for digital therapeutics. DTA is looking at what is the active ingredient of a digital therapeutic or the inactive ingredients of a digital therapeutic. Once we have that how do we start to create standards to ensure that those inactive ingredients are what they need to be and that the active ingredients have what they need to be. DTA could use those eventually to start to identify if there's a counterfeit product one day or if a product has been tampered with. Those are the kinds of ideas that were working on right now and we need to get there because at this point there are high-quality companies making high quality products. I think one day it could be easy for a company to come in and say, "We're a digital therapeutic too!" and create some code or tamper with someone else's code and they will be considered as a counterfeit digital therapeutic, but what kind of standards do we have that we could point to actually identify who is a counterfeit and who is not. Those are the kind of things DTA are trying to create now so one day we could point to it and have more reliability in the industry.

5. How about reimbursement system by payer in US?

Ms. Megan: A direct relationship does not exist in the United States. We can get as many products cleared by the FDA as we want but that doesn't mean a payer is going to think that that means anything to them. At this point we have to go to every single

payer individually and share with them our product, give them examples on what we are doing, prove our value; so we have to do a lot more work because we have to go to every single private payer or employer that we want have coverage and that's a lot of effort right now. We do have a public payer system and we have a private side in the US.

Digital therapeutics have only been on the private side for this point. On the public payer side, there is Medicare which is mostly looking at those who are older than sixty-five years of age and then there is Medicaid which is looking at people who are under the poverty line, so some Medicaid payers right now are starting to cover companies with very small numbers, like WellDoc. The Medicare side hasn't even looked at this, so right now they should go through the private payer system as opposed to the public payer system in the US.

There are many companies does not have reimbursement, even they got FDA approval. They cannot only go to one payer and assume that that will be all they need to do. It's a complicated system but they must determine who are the patients that they are targeting. If they are targeting Alzheimer's patients, for example, those are generally going to be older patients—the problem is Medicare is the group that covers them, because once they are over 65 that means Medicare covers them. If they have a digital therapeutic for a patient group who is usually aged eighty years of age, they may not have the ability to cover it right now because until Medicare says "Yes, we will cover these no private insurer is going to cover something" because it's not their patient population. Therefore, companies must know who you're targeting for your patients to know which payer type they have to address.

If companies address diabetes, people of all ages and types have, companies must look at those who are less than sixty-five years old, those who are older than twenty or what not. When they are very specific populations, they have to find out which payers cover those, and would cover that. However, patients can go from multiple insurance companies; every time they switch a job and get a new insurance company. There's a lot of times a patient will jump to different companies so it doesn't mean that an insurance company will have one patient for their life. Companies have to prove their value as a digital therapeutic product, or mHealth product even for a one to two-year span as oppose to an eight to ten years span because if people are going to move between insurance companies then the insurance company will only want to say, "I will only cover your product if you can improve their health and improve my budget in the next one to two years because I may lose that patient," so they don't cover it. Unlike a single payer system like NHS or MHLW where we have a patient for our whole life you can have longer spectrum, so we can say our product will affect

your patients in ten years. However, in the US, unless we can say it's going to matter in one year, it's going to be a lot harder.
Payer represents many employers. If we have national large-scale payer, they could put a digital therapeutic product on a formulary. They can put that on their formulary, but then that means that it doesn't necessarily mean that employers are automatically going to pay for that or add it into their bundle of coverage.
The prices generally are recommended by the company saying, "we think that this is what our products is worth based upon how much we spent in developing it", but also based upon cost savings that we know this will have" so it's very a complicated system to create a price but they will propose the price and then the negotiations start in the US.

6. What do you about obstacle or challenge in mHealth?

Ms. Megan: Digital therapeutics is a new category of medicine. There are both obstacles and opportunities. If we look at the design of a product, the validation of a product, the regulation, the coverage and implementation—there are those five buckets, designation, validation, regulation, coverage in terms of payments, and implementation that we have to address all of those issues and address aspects of everything in all five of those buckets.
When we work with the design with designers and developers, what do they need to consider is what certifications do they need to achieve as they design it. Looking at the validation, what types of trial do you create, what's the level of rigor across the board from both the clinical and health economic perspective. On the regulatory perspective, we have to figure out the SaMD criteria, and the user effectiveness guidelines, and how does Japan do things versus health Canada and are there similarities between those processes. In terms of payers, how do they value these, what value will they bring to their patients, what's the timeline of that, what types of criteria should they look for. On the implementation side, we have to deal with patients are being prescribed a digital product. That's never happened before. Healthcare providers are going to have to prescribed these; a pharmacist is going to have to incorporate this into medication reconciliation. There is a lot that we have to consider, the whole industry is full of obstacles and challenges but opportunities too. Designation, validation, regulation, coverage in terms of payments, and implementation, these all five buckets have their own issues, and all five are incredibly important to making this industry have some degree of cohesion throughout all five of those. Last point is iteration, as soon as we get to

implementation we go right back to design and then. It's a circular, it's not just a one-time process but there's a lot of nuances there.

Interview with Mr. Hermann

1. What do you think about mobile health innovation on your business?

Mr. Hermann: Our goal is to move more and more things to the home from hospital. mHealth become very important in terms of managing chronic disease, because it just depends on what the disease is, but if we can kind of do a continuous monitoring, or it doesn't have to be continuous, but maybe once a day we get some input, we can track, we can understand progress, we can potentially get warnings when things are going wrong. All of that's critically important. People that have diabetes always had to do a finger stick. And then they have got a little of device that reads that and tells them their sugar level. They now actually have a continuous monitoring version with the patch. It's a patch they wear, that's huge. The flip side is they have now got insulin pumps, that are also tied to measuring it, and then they simply pump the insulin directly into you without you doing anything, that's pretty huge, both of those, so I think that's example of what we are looking for more and more in chronic disease. But obviously diabetes is one of the most significant, because people can die or very bad things, so that's where people that's where the innovation occurred first, and there are some really great innovations there, that I think we'll see that spread, you know each disease has its own challenges, right, but we will see that spread more and more.

2. How do you choose digital technology in your hospital?

Mr. Hermann: There are four criteria; It's going to lessen the work for the doctors and nurses. Second is that it's going to improve care. Third one is how mature is the technology or stable company. Fourth one is cost. Now there are two significant types of technology, one is in the hospital, and the other one is moving from the hospital room to the home. At the Intermountain health, their chief strategy officer is has created a whole, what they call a virtual hospital and tele-monitoring service. And some of that is video calls, some of it is actually devices but they've developed. We can set up this hospital in a box at home, however more importantly, you will heal better at home. People do not do well in hospitals. And then there are also the risk of infection, in hospitals, is very great certainly compared to being at home. Therefore, medical doctor wants to get patient home, because it costs less, and patient will do better. Their goal is to move more and more things to the home, however mHealth can support disease management especially for chronic disease. If they can do a continuous monitoring or remote monitoring, they can understand

progress, and get warnings when things are going wrong.

3. Which specific regulation or guideline related to your business?

Mr. Hermann: Kaiser is a completely electronic company. We have one of the largest messaging infrastructures s the heart of Kaiser's electronic systems, with all of the messaging streams as the veins and arteries. A few data points about the volume of messaging—messages to and from EPIC, which is our EMR, are over 30 million per day. Their medical device integration project, which is just finishing, which automatically updates our EMR with vitals from the machines so now there's no person intervening. It's actually doing it electronically right from the machine, into the medical record. There are over 5 million messages per day there. Their API traffic is over 80 million transactions per day to our mobile application, and other system using APIs.

We use HL7 as their standard messaging format, because Health Language 7 (HL7) is the international standard for health information messaging. And then they use SNOMED (Systematized Nomenclature of. Medicine), just another data point. SNOMED is in the international clinical terminology as a global language for health uniting health system for around the world and enabling them to communicate and understand one another. SNOMED is maintained is developed and maintained as an international endeavor.

Standard is important to interoperable and secure data. Furthermore, standard will support the challenges how do we bring this information correctly from the home, or if it's a wearable or data taken by a doctor, taken by a device in the hospital, taken by a nurse that we put in your medical record. If we use standard, we consider that to be absolutely factual information.

4. Which players is the most key player in mobile health in US for example doctor, hospital, tech company?

Mr. Hermann: The most important player is physician but that combination between physician and the technology people on the maturity of the technology in the hospital or health care organization because again they have to be able to accommodate that information flow in some way. I think that doctors and entrepreneurs are the best. F The best ideas are nurse better than doctors, because nurses are all the time with the patients. The doctors come and go, but the nurses deal with them all the time,

There's actually a movement in the United States, called the maker movement. "Maker" means literally kind of building things, or using 3D Printing, or

experimenting. There's whole group called Maker Nurse, and some hospitals have created an innovation space in their hospital, for Maker Nurses. Kaiser Permanente have the Garfield innovation center in Oakland. The teams apply their field experience to explore new care solutions through hands-on simulations, quick prototyping, and technology testing. Successful initiatives evolve into pilot programs in Kaiser Permanente medical centers, clinics, offices across the nation – and sometimes even around the world.

5. What do you think about the trend of medical doctor entrepreneurship in mobile health?

Mr. Hermann: Doctors and entrepreneurs are the best. There's a lot of them. There is a conference called Exponential Medicine that's held each year that I got to attend one time, probably 50 percent of the attendees are, physician entrepreneurs. They are great but I mean the best ideas are nurses. So much better than doctors, because nurses, they are all the time with the patients. The doctors come and go, but the nurses deal with them all the time, there's actually a movement in the United States, that I found out about, there's something called the maker movement in the United States, it's been around for a long time. "Maker" means literally kind of building things, or using 3D Printing, or experimenting, you know, making things, well, there's actually whole group called Maker Nurse, and some hospitals have created an innovation space in their hospital, for Maker Nurses, I think it's the most brilliant thing you could ever do, because it's really amazing, if you go in, I'll give you one of example, and this is like the silliest thing , but it's brilliant, it's what only a nurse could figure out, ah, which is, ah, nurses were being bothered by people when they were giving medicines that that they needed to pay a lot of attention to.

6. Which specific regulation or guideline related to your business?

Mr. Hermann: Interoperability has been the goal in the United States. From the government, that started under the Obama administration quite a long time ago. About the same time, the ACA or Obama care came in, and it's been slow and hard, but, the electronic medical record level, is to be interoperable. The government is saying hospital must do this, and interoperability is a key component, of allowing that innovation to happen. And then, HL7, part of HL7 is FHIR, which is a new standard created by HL7—Fast Healthcare Interoperability Resources. It's so much easier to code, because it's basically the same kind of coding we do for web stuff, and ah it's just been embraced hugely and having that standard there for communication

in interoperability. I think will eventually increase innovation because again, the communication of the data is so critical. It's not a regulation, but it's a standard, and by having a good easy-to-use standard, he thinks that will help with innovation.

7. What do you about obstacle or challenge in mHealth?

Mr. Herman: Keep agility of innovation is a challenge on mHealth. There are some case that kind of Silicon Valley type of companies, enter health care, and they are invested billions of dollars, and then they suddenly realize health care is not like any other thing in the whole world, and so that slows down the innovation. It shouldn't slow down the innovation, the problem is we're talking about people. Recently, FDA is trying, figure out the most agile way to provide proper governance, and still encourage innovation, and the situation are getting a little bit better.

Interview with Dr. Merlo Pich:

1. What do you think about mobile health innovation on your business?

Dr. Merlo Pich: mHealth is Future of pharma, and mHealth will be change clinical trials. Clinical trials will be running different wave 5 years' time. Real time data very important because they can help the clinical team to get information immediately, from patient in case of adverse reaction, severe reaction, severe events. It can be very rapidly involved and support the patient that is joining in our study. The second very important point is that, pharmaceutical company has to help the development of awareness about the value and the relevance of the data and their privacy and related principle and share with the people that are involved in our clinical trial, the respect for this ownership. Basically, bring this to a level in which pharmaceutical company are having a full consent to work with their data. It is a different policy to work with a person. Until now, basically, you get data and then they disappear, but the idea is that we should help them to understand that they can keep this data in their database and then next year, 3 years' time or 10 years' time, this data may come back and be very useful for profiling the trajectory of the person.

2. I think mHealth is entry step to collect Health data. What do you think about health data with mHealth?

Dr. Merlo Pich: Aviation health is a very interesting company because they are building a business around the, in full consent, the consenting individuals that are sharing their own data, so those individuals are volunteering using an app or a phone or maybe a wristwatch. And they collect the data about their movements, or their daily activities, the sleep and so on. They put on the cloud and then Aviation health can ask for a full consent, " Can I use your data for a study for a clinical trial, are you interested to join clinical trial. This a very important way in my own opinion to build the new clinical trial of the future because it will be based on the willingness of people to participate, and to share the data that will be available. And building the four are very strong statistical package foresee the signal for efficacy. It's not only a democratic way to deal and a respectful way to deal with the people as a technologist's problem, but it's also a way to improve our capacity to see a signal of efficacy and justify this with payer, so we can basically build the pricing out of this. Pharmaceutical company should open the mind and maybe start a collaboration with people like this, or companies like this or maybe to startup companies like these in Japan, because this is something that is going to become important everywhere. Furthermore, there are potential data on paper transfer all this into digital, like

vaccination and then the pediatrician on the medical note. And then add to the smartphone. All the information coming from the various exam that we do and how we are doing. When we are in the train and then you play with games, we can record the performance of our games. we can show that our now previous baseline profile was more or less normal, and then you would see the difference so we can measure within ourselves the effect of a drug.

Cleveland Hospital is very advance not only they are using technology for their internal doctor. Several children hospital has already tablets. All information about the drugs interaction. When they are at the bed of the patient, they simply check the drug interaction, they check if the dosing is fine. One of the applications that they are using is Epokrates. Epokrates is the oldest physician in western world. We see the result of this kind of information that we can get, bill ID, IDC 10 for the classification of (inaudible) guideline for the treatment so it's a very useful device that we will bring in the bed, and then we can go on drugs. Those are very updated, and we can manage the risk associated with this.

3. Which players is the most key player in mobile health in US for example doctor, hospital, tech company?

Dr. Merlo Pich: Patient is key player. They are the main player these days because a very important role of the technology and they want to produce the technology making more and more efficient. Unfortunately, the Google, Amazon and Apple of this world they tend to have a major hold. Furthermore, role of politics in health care is also important. In particular but the regulator in the politics. Because they are fixing limits on what we can do with the technology and sometime there is an unintended effect of the rules that are made to protect people. We have this perception that for example, Amazon and Google, and everybody will be listening our, or Apple, our Siri, when we talk with our artificial intelligence. They will store, then record this one, then they rebuild our profile, they imitate our voice, then they can substitute for us. And this paranoid tendency is really something true because we don't understand when we go and you sign for, and for example the cookies, it's so complex. Every company is slightly different. When we get in, we have to be fast because we need information and then the site said, "Did you sign in for the cookie policy?" and then you have to go through 25 pages, and which is very difficult to understand what is there. This is made by lawyer to protect the company, not made by us to choose what to do. Few of them they do good job and I have to say that some are really good but there are some that you go through several pages and you don't

understand where the ending is. If we really want to go along the line to use those technology for real world evidence generation, we need to make clear that if we are recording something this is done in a way that is going to help them to build their own database properly and we will be transparent 100% on where the data goes. He thinks FDA is very supportive, and then the European agency is the same.

4. What do you think about the trend of medical doctor entrepreneurship in mobile health?

Dr. Merlo Pich: Companies that are startup without medical entrepreneur are not bound to win except if they have an exceptional engineer that is devising something very unique.5, 10 years ago, the company starting up without medical expertise, could still do something but now, it's impossible. Competition is too high, there are more than 200,000 apps/digital devices that is being proposed to make a difference. The majority of them is being generated without medical knowledge, the patients' needs, Knowledge of how the solution and the therapeutic can be distributed and then knowledge about the context in which this is done. If he/she does not know all of this, he/she just building up an app that's not going to help.

5. What do you think about FDA on mobile health?

Dr. Merlo Pich: 100 percent. FDA is very supportive. The interaction we had with them was only one, but was very positive, actually they said, "Please go back with us with your digital plan because we are really curious to see what you're doing." Because we went there just to present some of the portfolio assets, investment, and the way we would like to do it and we quote digital and they say, "Well, why not you come back," which I was very happy about. And then the European agency is the same. I had an informal meeting with the European is called Innovation Task Force. The Innovation Task Force is about all the future technology that can go through. And they are super interested to hear our opinion how to apply this technology and they're actually waiting to learn from us. It's a, that's why, but a pretty competitive consortium we can go there and say "Yes, we have company. We are 9 companies in this consortium, we are leading by the way, and this is our idea, how to do things, what do you think?" and they will feed us back. We can bring it back to the company and also to the consortium and say "Let's go in this direction and do the next step. Start this in that way." And this is going to bring back to all companies the same endpoint. We are kind of building a context, in which not only the FDA but maybe also the Japanese, regulatory in the near future they will be able to.

6. Are there any criteria for technology selection for clinical trials?

Dr. Merlo Pich: Absolutely. Now, there are several. This is a pretty rich area that is becoming bigger and bigger over time and for us, for example, what is important when increasing the efficiency of clinical trial. And efficiency means several things. First of all, higher probability to see a signal of an effect of the drug. And the other one is reducing the cost and reduce the burden of the subject that is involved. Sometimes, they undergo a lot of tests, a lot of major changes in his way of living, because of the treatment, and some cases are fine, but some cases are not, you know. Depends very much on the condition of the subject. If you are in Oncology and you discover you have a cancer, you do everything to do something. You don't care, you're super motivated. But if you have a chronic disease, for which you have the third treatment, and it doesn't work, you can lose interest. It's much more difficult to keep this one in the study and keep them motivated. We have already a different world that needs to be engaged in. So, the criteria for choosing the m-health/technical device/digital technology, depends on the condition of the subject and the disease that he has. It needs to be tailored with the symptom. You cannot have a technology of course for everyone. I mean, you may have it one in which push message, with questions, and it pops out. It's called ecological and momentary assessment. It's quite useful because it's telling I don't need memory and I know how I feel now so I can't write it. A bit invasive, because if we are talking now, I'm talking with you, and something is popping out, so, how do you feel? Annoyed by you because it's kind of interfering with your life but on the other end, the young generation are very often the, their social network on all the time, and they are multitasking, so it may work. You know, particularly for the younger generation. But this can be applied to any disease because I'm asking how you're doing and feeling so I can build this patient reported outcome for the disease. But in other case, if I'm monitoring movement, for example, I am using phone for monitoring movement but actually what I would like to monitor is my after, you know the, the ends because I train or something, this is not good. I need something specific. And the, again, if my voice for example is going down because of a rare disease. My voice is stuttering and when I'm stressed it becomes more and I have to find ways to, microphone or something to collect this information. It's definitely depending on the symptom. You know, so you have to fit. The technology should fit the symptom that you want to follow and should fit the global need of the subject and then availability of the subject to use this technology. This is the reason that passive technology is preferable. Technology that work behind that you do not realize, that is actually there. Counting the number of phone calls or assessing social interaction.

7. Which specific regulation or guideline related to your business?

Dr. Merlo Pich: When we prepare an IMI proposal, the European Commission asks us to list the documentation that we are using to support the proposal. And several are, most of them are regulatory-driven documents so like they are using as a guideline or guideline from international

association/medical association or the American one that are set in the ground how to diagnose, or how to treat/which is the best treatment for the subject. So those guidelines are the building block of the clinical study that we are proposing. We have to make them explicit. And is one full page of guidelines, We build this together with several colleagues from pharma, from academia, for our digital clinical study,

8. What is the Challenge for pharmaceutical company with technology?

Dr. Merlo Pich: Digital technology is different from the comfort zone which pharmaceutical are. Sometimes, digital technology may have made them uncomfortable. And also, several clinicians, and some academics, they didn't like because it's kind of different from the comfort zone of traditional pharmaceutical products. Same thing with commercial. Commercial, at least the traditional one, the digital is technology, it is Google stuff, and it's not pharmaceutical company. The clinicians and the academics sometimes say, "It's such an imprecise measurement, you need one million people to produce their own opinion, have to trust what is the outcome." Therefore, pharmaceutical company would never be able to use it because this is chaotic. Furthermore, there was this negative appreciation and saying they will not use it, this is so unspecific, this is consumer-grade thing is not research. There is this kind of obstacle that is perceived like a not precise, not scientific, that's just commercial kind of technology that is much closer to a gadget than the real science. Accordingly, pharmaceutical company have a position by hard-nosed scientist, hard-nosed commercial for different reason. Pharmaceutical company may have some cultural problem in implementing it because of the understanding of the details. Lack of understanding, lack of knowledge about what is the digital data, digital ethics behind it. Therefore, there is at times a bit of confusion and suspiciousness around that. On the other end, there is opportunity. However, some startup company are overselling digital technology without data, evidence, and science. It only cost, it does not lead to anywhere, that's why pharmaceutical company need to build the science how to understand this technology. The major problem is this lack of knowledge and the feasibility that the decision is driven.
The last one is a person. It is very important that the qualification of the people that are going to advise for engaging and investing in digital health with knowledge to build on data that are collected in an appropriate manner. The culture, the capacity to understand the problem and the people that can do their duty, it's very critical.