The Global Digital Therapeutics Industry Report 2022

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1. Overview of Digital Therapeutics

Digital products are changing our lives in all aspects along with the rise and maturity of Mobile Internet. So does in the healthcare field. Based on the development of digital technology, Telehealth, smart hospital and other scenes, which could only appear in the vision, have come true one by one. Besides, another scene, which was once considered as a vision, is gradually becoming a reality - now, we can download an APP for disease treatment according to the doctor's prescription. APP will also become a drug form. It may work on its own or be combined with drugs to bring more efficient and accessible treatment. It is the "Digital Therapeutics (DTx)", which is highly concerned by the whole industry at present.

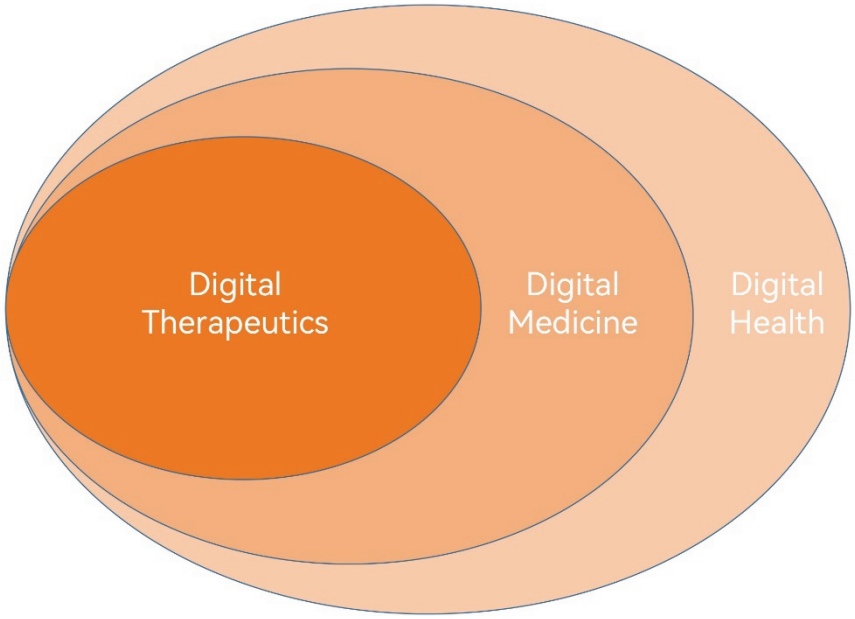
1.1 Definition and key features of Digital Therapeutics

What is Digital Therapeutics exactly? What are its definition and key features?

1.1.1 Definition of Digital Therapeutics

First, what is the definition of Digital Therapeutics? Based on different considerations, different organizations have different emphases on the details of this issue. In our previous white paper, Digital Therapeutics has been defined in combination with actual situation in China: Digital Therapeutics is a treatment or intervention provided to the patients on the basis of evidence-based medicine. These interventions are driven by high-quality software programs, of which the essence is the digitization of some heathcare services and the key function is to prevent, manage or treat a medical disorder or disease. They can be used alone or in combination with drugs, devices or other therapies.

Relationship between Digital Health, Digital Medicine and Digital Therapeutics



Digital Therapeutics conceptually overlaps with Digital Medicine and Digital Health. They are actually in containing relation layer by layer, namely, Digital Health > Digital Medicine > Digital Therapeutics. Digital health has the broadest definition. Besides patients, Digital Health also targets healthy people, including intervention in consumers' lifestyles, health management and other health-related technologies, platforms and systems. Digital Medicine is a technology, platform or product, which focuses on specific group of patients, conforms to the concept of Digital Health, is evidence-based and is suitable for medical processes. However, it does not necessarily adopt software-driven intervention and treatment measures. Digital Therapeutics is a therapeutic which conforms to the concept of digital medicine and is driven by software to prevent, manage or treat diseases. At present, Digital Therapeutics is still in the stage of development and exploration. According to specific situation of each region, the definitions of the above three terms overlap to varying degrees in areas where Digital Therapeutics has not been strictly defined.

1.1.2 Key features of Digital Therapeutics

According to the definition of Digital Therapeutics, it is easy for us to summarize key features of Digital Therapeutics: serving patients; evidence-based; treatment or intervention measure; and driven by software and used separately or concurrently.

Serving patients: First of all, it is important to clarify that the service clients or users of Digital Therapeutics should be Should be patients or their family members. On the basis of serving patients, it may also serve doctors at the same time; However, sole service for doctors, such as helping with efficient diagnosis, decision-making and patient information management in the process of disease treatment, is not included here.

Evidence-based: there is no doubt that Digital Therapeutics is supported by evidence-based medicine rather than empirical medicine. Its efficacy must be based on evidence.

Treatment or intervention measures: the treatment or intervention measures provided by Digital Therapeutics may produce a certain effect on physical status of patients or natural development process of diseases, to realize the functions of preventing, treating or managing certain diseases.

Driven by software: it means that main functions of Digital Therapeutics to achieve treatment or intervention should be provided by digital technology of software, such as pictures, videos or virtual environment. Of course, the software should also meet various functional and regulatory requirements.

Used separately or concurrently: Digital Therapeutics may appear separately as a common APP on mobile phones, a desktop application or even a browser application. Moreover, it can also be combined with hardware, other software and services. However, in the case of combined use, specific classification should be determined according to specific conditions and requirements of each region.

1.2 Pain points solved by Digital Therapeutics

Digital Therapeutics springs up mainly because of shortcomings of traditional medical methods. As a supplement and optimization for traditional treatment methods, Digital Therapeutics mainly solves many pain points faced by patients, healthcare providers, payers and pharmaceutical enterprises.

1.2.1 Patients

Digital Therapeutics mainly focuses on patients. Therefore, it should solve many problems faced by patients, including improving accessibility, adherence and experience, providing personalized treatment, improving the quality of life and reducing the cost of medical treatment.

The rise of Digital Therapeutics is mainly stemmed from the rise of various digital technologies based on Mobile Internet. Most Digital Therapeutics are based on Mobile Internet technology. Patients can download and use Digital Therapeutics at any time, which greatly improves the accessibility of medical service. Some Digital Therapeutics may not rely on Mobile Internet technology, but the empowerment based on digital technology has greatly improved the service capacity of healthcare providers and the accessibility of medical services to patients.

How to improve patient adherence has always been a great problem in the treatment process -the main reason for poor efficacy often lies in poor patient adherence. It has been proved that patient adherence cannot be improved by manual means successfully. However, Digital Therapeutics can actively remind patients through digital technology and improves patient adherence from multiple aspects, such as UI improvement, patient education and incentive mechanism; Moreover, manual intervention is introduced when necessary, which can effectively improve patient adherence.

Hospital visits have to experience the inconvenience of long-distance travel and crowded queuing, while Digital Therapeutics can enable patients to receive consultation and treatment at home, so that the experience could be greatly improved. In addition, Digital Therapeutics can better protect the privacy of patients with mental and cognitive health problems and improve their clinical experience. Therefore, it can further improve the probability of such patients seeking treatment and reducing doctors’misdiagnosis caused by patients consciously concealing their true medical condition for fear of the shame.

Due to the lack of data, traditional ways may not achieve personalized treatment, or may make it by right of a great cost, so that gains cannot make up for losses. Combining with hardware, Digital Therapeutics can collect and analyze users' basic data more easily than before and provide users with an individualized therapeutic. Digital Therapeutics can indirectly reduce costs by improving efficiency or expanding service capacity. Because Digital Therapeutics is based on software, its cost is generally lower than that of manual therapeutics. In addition, if accessibility, adherence, user experience and individualization are taken into consideration, cost reduction of Digital Therapeutics is more considerable.

1.2.2 Healthcare providers

For healthcare providers, Digital Therapeutics can mainly improve service efficiency, patient satisfaction, data acquisition and auxiliary capacity and reduce service costs.

With various digital technologies, Digital Therapeutics can greatly improve the accessibility of medical services, prompt doctors to give active intervention at an appropriate time and further improve the service efficiency of them by improving the efficiency of single medical service or expanding service capacity. In addition, Digital Therapeutics can also improve patient adherence, provide data-driven personalized treatment and provide doctors with auxiliary diagnosis function based on medical principles and data analysis model, so as to improve the diagnosis and treatment efficiency of healthcare providers.

Digital Therapeutics can help medical institutions improve their service capacity and serve more patients under the same conditions, so as to reduce the cost.

Digital Therapeutics improves the accessibility of services, so that patients can receive medical services at home and directly communicate with medical staff when needed. Through Digital Therapeutics, the patients can more clearly understand their condition and obtain individualized treatment regime. In addition, Digital Therapeutics is also helpful to reduce medical costs. All these will improve patients' satisfaction.

Digital Therapeutics can more easily obtain the health data of patients outside the hospital; meanwhile, it can realize continuous collection of health information. This will greatly make up for the hospital's lack of patients' data outside, to better realize the whole process management of prevention - diagnosis and treatment - rehabilitation. Besides, the information collected by Digital Therapeutics covers multiple aspects, such as patients' physiology, psychology, lifestyle and natural environment, which can collect more real-world data for clinical scientific research so as to improve the cognition and scientific research ability of diseases in the industry.

1.2.3 Payers

For the payer, Digital Therapeutics may play the role of intelligent insurance underwriting and expenditure control. The payer can also develop new products on the basis of the data collected by Digital Therapeutics. In addition, for commercial insurance and other similar payers, Digital Therapeutics can also play an important role in promoting customer approaching and renewal.

As the payers of medical services, health insurance or commercial insurance enterprises or the enterprises paying insurance premiums for employees are most concerned about how to control expenses. Digital Therapeutics can intervene users' lifestyle and also play a certain role in disease prevention, accordingly reducing the incidence of diseases and the compensation of payers.

With the development of domestic insurance market, insurance products for mental and cognitive diseases will be the next blue-ocean market. Digital Therapeutics can quantify mental health condition to some extent and accordingly provide intelligent underwriting means to help payers and policyholders quickly decide whether they meet the insurance conditions, which reduces the risk of

payers.

The exploration of health insurance for non-standard entities has attracted wide attention in the insurance industry. Digital Therapeutics collects a large number of health data of the patients with chronic diseases, which can be used in actuarial model by commercial insurance companies to develop innovative insurance products and enable more people to benefit from insurance.

Digital Therapeutics can intervene early in the links of early detection and chronic disease intervention and realize continuous monitoring. The final results may awaken patients' concerns about the disease and then become interested in targeted insurance products to help commercial insurance enterprises in the fierce battle of market share to get customers or renewal in the future.

1.2.4 Pharmaceutical enterprises

For pharmaceutical enterprises, Digital Therapeutics can improve the accuracy of drug administration and the adherence of products. Moreover, the patient data collected by Digital Therapeutics is also helpful for pharmaceutical enterprises to realize precision marketing and provide references for follow-up R&D and evaluation.

.The response to treatment with medication varies from person to person due to a variety of factors such as physical condition, age, genetics, and concurrent use of other medications. In the past, it was difficult for us to realize individualized drug therapy. By assessing the patient's actual condition, Digital Therapeutics can provide patients with personalized dosing regimens that can improve dosing accuracy, enhance drug efficacy or reduce toxic side effects, and reduce healthcare costs.

Digital Therapeutics may regularly remind patients to take medicine and improve patients' medication adherence through incentives and other ways. Digital Therapeutics combining software and hardware can also track the medication of patients to a certain extent - through real-time monitoring and feedback of sensors, healthcare providers or caretakers can also know whether patients take drugs on time and correct patients' behavior when necessary.

Besides realizing individualized administration and improving medication adherence, Digital Therapeutics can also monitor the use of patients' drugs and consumables, timely capture their potential needs and realize precision marketing through message notification and delivery service on the premise of legal compliance.

Digital Therapeutics can provide pharmaceutical companies with unprecedented data that goes far beyond randomized controlled trials. By providing pharmaceutical companies and doctors with real-time results of patients and through accurate and standardized big data, Digital Therapeutics can continuously provide powerful auxiliary functions, which can be used to improve treatment and even create new products.

1.3 Technology-empowered Digital Therapeutics

On the surface, Digital Therapeutics involves only software technology, but it actually involves a large number of digital technologies behind it, such as wireless networks, sensors, microprocessors and integrated circuits, artificial intelligence, cloud computing and big data, VR/AR/MR technologies, etc.. The empowerment of these digital technologies has also laid the foundation for the realization of Digital Therapeutics products.

1.3.1 Artificial intelligence

Traditional medical services are provided by doctors on the basis of their expertise and experience. Digital Therapeutics, on the other hand, precipitate the knowledge and experience of physicians and digitize the service.. Artificial intelligence can be seen everywhere in the whole service process and empowers Digital Therapeutics from many aspects, e.g. personalization and proactivity[1]. Meanwhile, Digital Therapeutics also needs to be self-driven, able to act as a proxy for doctors to interact effectively with patients to some extent, and they also need the support of artificial intelligence behind them..

Using artificial intelligence and machine learning systems, Digital Therapeutics can monitor and detect symptom data of an individual patient in an adaptive clinical feedback cycle by right of digital biomarkers. Artificial intelligence can learn and predict effective interventions to provide more individualized therapeutic regimen through multi-dimensional data[2]. In this process, it requires to turn the expert experience and consensus summarized from the traditional clinical process into clinical knowledge maps of different guide types and make them automatic in the service process through artificial intelligence learning. So, it has a high threshold.

Proactivity is also one of the benefits of Digital Therapeutics given by artificial intelligence. Based on the predictive analysis ability of artificial intelligence, Digital Therapeutics can intervene faster and more efficiently to prevent unnecessary emergency care - for example, artificial intelligence can learn through knowledge graphs to prevent emergency adverse events caused by drug interactions. Patients, payers and already overburdened hospitals can benefit from it[3]. On the other side, every piece of data shared by patients also provides a steady stream of materials for the learning of artificial intelligence, which will help to improve the prediction ability of artificial intelligence to better predict the potential needs and challenges of patients according to their multiple features (age, gender, drugs, etc.).

However, frankly speaking, artificial intelligence currently used in Digital Therapeutics mostly uses general fixed algorithms, which can only provide limited individualization and may not provide

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1 Adolfo Eliazàt: The Role of AI in Digital Therapeutics (https://adolfoeliazat.com/2021/09/14/the-role-of-ai-in-digital-therapeutics/)

2 Palanica A, Docktor MJ, Lieberman M, Fossat Y. The Need for Artificial Intelligence in Digital Therapeutics. Digit Biomark. 2020;4(1):21-25. Published 2020 Apr 8. doi:10.1159/000506861

3 Zhang Qiang, Microsoft (China), Overview of the Microsoft AI National Program

adaptive intervention completely based on the unique individualized patient symptom data[4]. Therefore, the artificial intelligence of Digital Therapeutics should focus on realizing more adaptive algorithms and more flexible interventions via machine learning in the future. Namely, artificial intelligence and machine learning enable the system to automatically learn from the data and adjust the output and to perform tasks similar to human beings without explicit programming. It is undoubtedly a huge challenge for the artificial intelligence industry.

1.3.2 IoT

It is mentioned in the definition that Digital Therapeutics can be used alone or in combination with hardware, other software and services. Among them, the reason for combination with hardware is mainly that data-driven digital therapeutics should collect a large amount of data to achieve better effect. The data colllection and transmission relies on IoT devices to a large extent, including wearable devices, smart home monitoring devices and so on.

The concept of IoT was put forward at the time when the global health costs were rising rapidly, so that IoT was quickly adopted by the healthcare industry. It has always been considered that IoT can effectively increase the income and reduce costs in the healthcare industry, provided that the data collected and generated by IoT devices can be turned into operational insight. Digital Therapeutics can really make effective use of the data collected by IoT - it may be used in the treatment process or reserved for research and development. It can be said that Digital Therapeutics and IoT are ideal perfect partners.

With IoT empowerment, Digital Therapeutics can greatly broaden the breadth and depth of its application. Firstly, IoT combined with medical devices can automatically and continuously collect and transmit physical information of the patients, enable Digital Therapeutics to monitor the patient's physical status and adjust the patient's behavior in real time; so as to improve the speed and accuracy of diagnosis and treatment and help to carry out real-time remote nursing for patients. Secondly, IoT combined with AI enables Digital Therapeutics to streamline clinical processes, information and workflows through automation, improving communication between patients and healthcare providers, within healthcare providers and between healthcare providers, so as to improve the operational efficiency and effectiveness of healthcare providers and improve the patient experience.

However, the management of IoT devices is not an easy task.. The management of all IoT equipment follows the cycle of "plan - pre-configuration - configuration - monitoring - retirement". The focus of each cycle is different. In the planning stage, the equipment should be grouped and access controlled according to the needs of the organization. The pre-configuration stage mainly involves security certification equipment to realize pre-configuration management and service pre-configuration.

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[4] Palanica A, Docktor MJ, Lieberman M, Fossat Y. The Need for Artificial Intelligence in Digital Therapeutics. Digit Biomark. 2020;4(1):21-25. Published 2020 Apr 8. doi:10.1159/000506861

Configuration is to provide updates, configurations and applications to assign the purpose of each device. During the monitoring phase, the device catalog, operational status and security need to be monitored, while providing proactive remediation of problems. Finally, equipment should be replaced and decommissioned in case of failure, upgrade cycle or expiration of service life. With the expansion of the scale, digital therapeutics enterprises should access and manage more and more IoT devices and then further enable them through application to realize business analysis and other functions. Besides gradual functional increase, aspiring enterprises should also consider internationalization in the future[5]. It is a great challenge for multinational enterprises, without mentioning digital therapeutic enterprises in infancy. The good news is that many IoT platforms can provide mature services and have many successful application cases. At present, network operators, such as China Mobile, China Telecom and China Unicom, have carried out a lot of work on IoT access management, and major cloud computing service providers, such as Alibaba Cloud, Tencent and Huawei, have also provided corresponding access and management services.

These IoT platform services can mainly solve pain points of seamlessness, security, intelligence and scalability. Firstly, for seamlessness, the platform services can help pre-configure solutions and SaaS and accelerate the implementation of the most common IoT scenarios and partner solutions. Secondly, these services provide reliable and comprehensive security for mobile and static data from the edge to the cloud. Thirdly, the platform can intelligently monitor equipment operation and predict maintenance. Finally, scalability can help developers quickly and simply expand the scale and region.

1.3.3 Cloud computing and big data

Data-driven is an important feature of Digital Therapeutics, with mobile apps as one of its main manifestations and evidence-based medicine as one of its cores. It is rightly because of the gradual maturity of cloud computing and big data applications in recent years that Digital Therapeutics has developed rapidly. Cloud computing and big data have been playing an important role in the operation management, clinical scientific research, iterative development, intelligent services and other aspects of Digital Therapeutics.

Behind Digital Therapeutics, the artificial intelligence can provide intelligent services and the logic is the knowledge graphs based on big data and the AI-aided diagnosis ability based on deep learning. For example, Digital Therapeutics can mark the contradiction between patients' health status and drug prescriptions and timely remind patients and medical staff in case of any risk of medication errors. In addition, in virtue of big data, Digital Therapeutics can remind and focus on high-risk groups, analyze and formulate corresponding prevention plans to prevent patients' conditions from deteriorating, and provide emergency services when needed.

One of main features for distinguishing Digital Therapeutics from Digital Health and Digital Medicine

[5]Tang Zhiyin, Microsoft (China), *Overview of Microsoft Azure IoT*

is that the former is evidence-based. In the context of big data, cloud computing, distributed storage, natural language processing and other big data application technologies are becoming more and more mature. The standardized big-data application based on patient data is combined with data mining and intelligent analysis methods to effectively establish scientific research ideas and methods based on real-world data and data-mining technology, thereby enabling long-term clinical research on Digital Therapeutics.

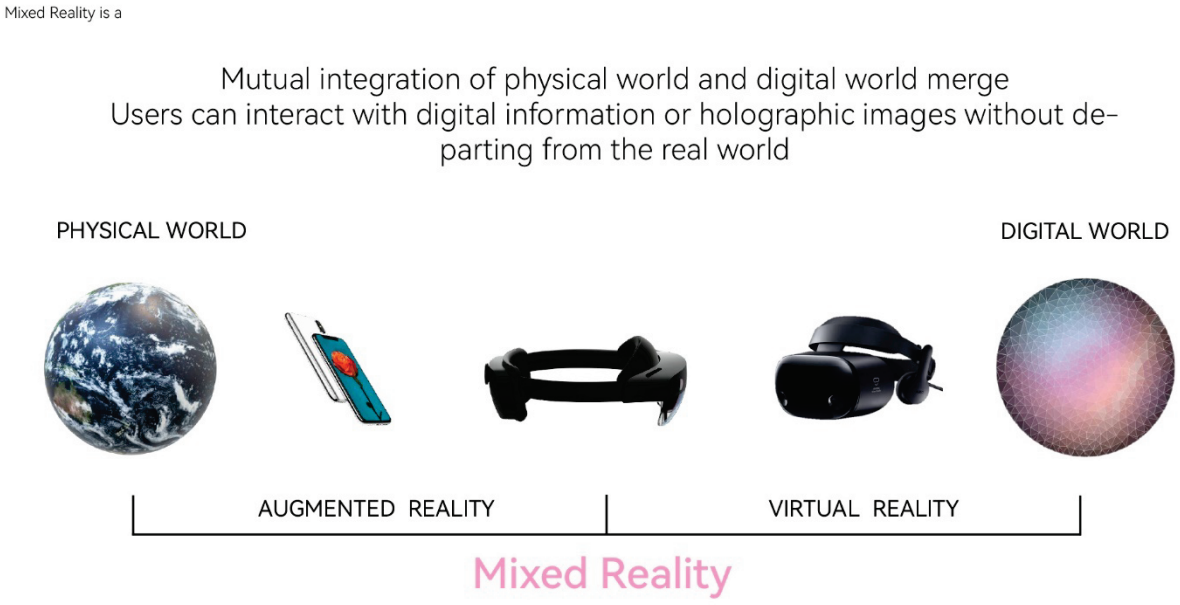
Big data also lays a foundation for the operation and management of Digital Therapeutics. The analysis on users' use can make Digital Therapeutics perfect day by day through rapid iteration. In addition, as data is recognized by the state as a market element, it may also be allowed for trading after compliance processing in the future. With the help of big data mining and analysis capabilities, it may be possible to find new business models in Digital Therapeutics.

1.3.4 Virtual, augmented and mixed reality

Virtual Reality (VR), Augmented Reality (AR), and Mixed Reality (MR) are a family of concepts collectively known as Extended Reality (XR). Along with the development of computer 3D display and the research of behavioral psychology and other disciplines, these concepts can bring people to an interactive virtual environment only by special sensing devices, such as stereo glasses and data grips (gloves). With the development of technologies and concepts, this concept has evolved from VR to AR, and then to MR. VR is a computer-generated 3D virtual environment that allows users to immerse themselves in it. The entire environment is purely virtual and is isolated from the real environment. AR is the addition or removal of virtual objects or information generated by a computer in real time that can be interacted with in a real environment, i.e., virtual digital images combined with naked-eye reality.. MR can be regarded as the combination of VR and AR. It is conceptually similar to AR and is a mutual mix of real environment and virtual environment; However, it is similar to VR in the terms of combination means, and combines reality and virtualization through digitally generated and interactive digital interface.

Relations of VR, AR and MR [6]

[6] Kong Ning, Microsoft (China), *Hololens 2 Overview*



XR has a long history of medical use. In addition to surgical teaching and navigation, XR is also widely used in cognitive-behavioral therapy to enhance its effectiveness - an "exposure therapy" that exposes patients to a variety of immersive scenarios that they gradually tolerate and adapt to. As the technology tends to be mature and costs fall down gradually, XR is largely introduced into Digital Therapeutics. XR has the advantages of realistic experience, intuitive and effective, reproducible and adaptable to remote treatment. At the same time, virtual reality exposure therapy using XR is more controllable than traditional exposure therapy (real-life exposure, imaginary exposure, etc.), with pre-set intensity and frequency, as well as more timely data acquisition. Therefore, XR can play an important role in the Digital Therapeutics of mental and psychological diseases[7].

XR combined with Digital Therapeutics can realize virtual reality immersive psychological education and solve relevant problems. XR is essentially very suitable for passive psychological education. It can create an immersive experience to carry out effective psychological education for patients. Virtual reality is considered as a powerful educational tool because it allows users to experience the environment rather than just learn to perceive the environment. Therefore, XR is more advantageous than traditional therapy. For example, the XR intervention teaching recently developed for depression can effectively encourage the mental health growth of teenagers.

XR combined with Digital Therapeutics can realize behavior activation and physical exercise. In addition, XR can provide users with a special environment to correct their habits. It can also be used

[7] Lindner P, Hamilton W, Miloff A, Carlbring P. How to Treat Depression With Low-Intensity Virtual Reality Interventions: Perspectives on Translating Cognitive Behavioral Techniques Into the Virtual Reality Modality and How to Make Anti-Depressive Use of Virtual Reality-Unique Experiences. Front Psychiatry. 2019 Oct 31;10:792. doi: 10.3389/fpsyt.2019.00792. PMID: 31736809; PMCID: PMC6836923.

for smoking cessation, conversion disorder treatment and physical rehabilitation.

XR can also lead to better cognitive reconstruction for Digital Therapeutics. Traditional cognitive exercises require patients to imagine a scenario and extract and manipulate from it for exercise purposes.. It is quite abstract for patients. XR can let users permeate into virtual scenes and actually manipulate these objects by using handles (gloves). It can change the silent nerve of the patient from passive to active to accelerate the remodeling of damaged nerve function; so as to exercise executive, memory, discrimination, observation, judgment, spatial positioning, abstract thinking and attention abilities of the patient and finally help them recover from the disease.

Social skill training is a general cognitive behavioral therapy. XR is very suitable for training social skills through virtual session agents and immersive scenes to improve the efficacy of Digital Therapeutics. For example, VR designs different scenes to teach children with ASD to learn common sense of life, such as crossing the road, shopping in the supermarket, etc. This experience can improve the life ability of children with ASD and give them confidence to engage in basic daily life.

At present, VR technology is widely used in Digital Therapeutics. There are several reasons: firstly, VR technology is most mature in consumer entertainment applications, which is consistent with the expression form of specially designed games in Digital Therapeutics at this stage; Meanwhile, VR solutions are relatively mature, and major VR equipment manufacturers, such as HTC, Oculus, Sony and Pico, can provide relatively perfect technical support and integration services. Moreover, its integration difficulty is relatively low. Along with further combination of Digital Therapeutics and XR technology, MR integrating physical reality and virtual reality will gradually attract people's attention. It should be said that Microsoft Hololens is one of the most mature MR integration protocols in the industry. It can provide cloud services and expansion capabilities by combining Azure cloud services and has been widely used in the fields of manufacturing, automobile, building and construction, higher education, retail and medical health[8].

1.3.5 Low-code development

Although so many digital technologies can empower Digital Therapeutics, it doesn't seem to be as simple as expected for start-ups to truly empower Digital Therapeutics with these technologies. As a product spanning many disciplines, such as medical treatment, medicine and equipment, software, big data, psychology and patient behavior research, the development of Digital Therapeutics has a certain threshold, especially for start-up teams with limited resources. To help teams focus their limited efforts and resources on the most core aspects, the industry also has a plethora of integration solutions to adopt. One of them is undoubtedly the low-code development, which has been popular recently.

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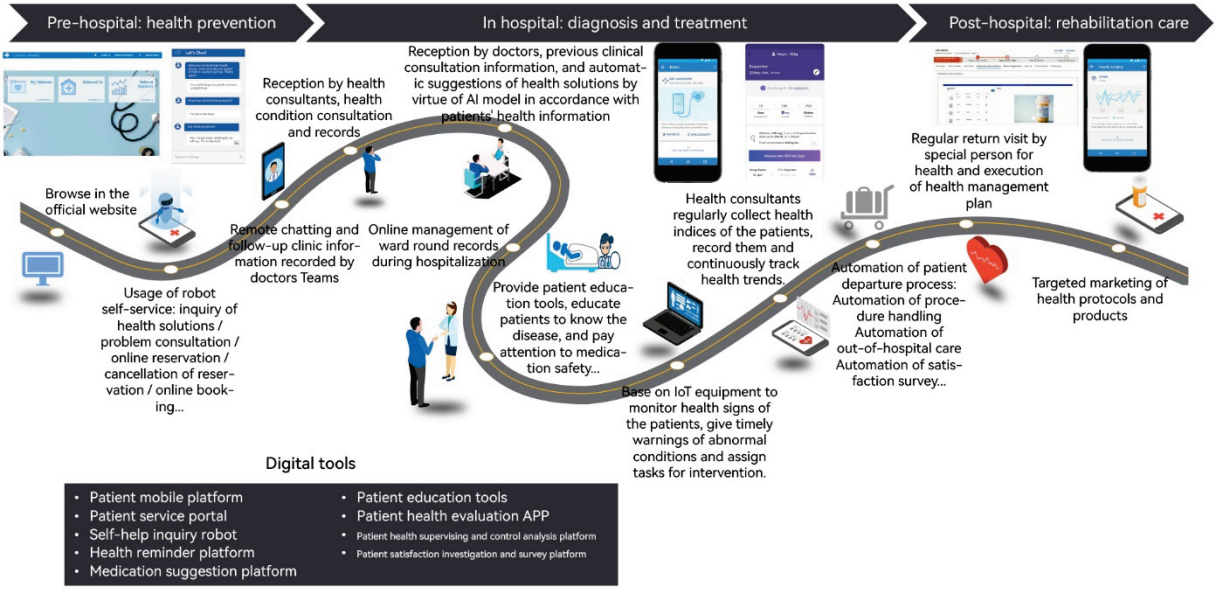
[8] Kong Ning, Microsoft (China), *Hololens 2 Overview*

Low code helps digitally manage patient processes and improve service satisfaction of the patient. [9]



Low-code development is an emerging cloud computing and software development technology in recent years. By visual dragging, application software developers can develop applications that meet their own needs even without relying on traditional professional programming. Visual programming is not a newly sprouted thing, which has been used by such tools as Visual Basic (a professional development software) for a long time. Nowadays, low-code development in turn further lowers the threshold for software development, bringing new experiences to the development of lightweight applications and the wider non-professional development population. Low-code development integrates a large number of existing modules for developers to call, thus reducing the requirements for development and greatly improving the development speed. Under the traditional development mode, in order to add artificial intelligence capability to software, the API of related class libraries must be called for further development, and statements, instrument panels and workflows also need to be further developed. However, on the low-code platform, it is only necessary to directly call the corresponding modules - for example, artificial intelligence capabilities are obtained by calling artificial intelligence and chat robots. On the similar low-code platform, the contact experience can be optimized in each link of "pre-hospital - in-hospital - post-hospital" and the digital management of patient process can be achieved, so as to simplify the business operation, automate the internal operation process, improve the efficiency of teamwork and external services, and improve the patient experience[10].

It is worth pointing out that low-code development is not a master key, especially, Digital Therapeutics has the attributes of medical devices, requiring consideration of all aspects such as data security,

[9] Sang Lulu, Microsoft (China), Power Platform Industry and Scenario Specific Protocol Map

[10] Sang Lulu, Microsoft (China), Power Platform Industry and Scenario Specific Protocol Map

privatization deployment, and future expansion, and it still needs to weigh whether low-code development is introduced throughout development. However, undoubtedly, it is a wise choice to introduce low-code development in specific period or specific process and consequently energize Digital Therapeutics.

2. Current situation of global Digital Therapeutics industry

At present, Digital Therapeutics is still in the initial development stage. The development of any industry can't do without the impact of multiple factors. As a rule of thumb, the rapid development of Digital Therapeutics industry requires the assistance of policies, market, capital, supervision and other factors. Therefore, sorting out these factors is helpful for us to better know the current situation and future development trend of Digital Therapeutics industry.

2.1. Rise of Digital Therapeutics around the world

Since the 2010s, Digital Therapeutics has begun to take shape in the United States and has gradually developed. With the approval of Pear Therapeutics' ReSET for substance abuse and alcohol abuse disorder in 2017 by the US Food and Drug Administration (FDA) in the form of "Innovative Medical Devices (De Novo)", more countries and regions have begun to focus on Digital Therapeutics and drive practical progress in this field. In addition to the United States, Europe, represented by the United Kingdom and Germany, and East Asia, represented by China, Japan and South Korea, have also been actively explored in Digital Therapeutics.

2.1.1. United States

As the leader of the third industrial revolution, the United States is open to the understanding of information technology and the combination of its introduction and use. The whole industry is aware that digital technology represented by the Internet has great potential to reshape medical treatment and is increasingly applied to the field of medical treatment and health. After many years of penetration of telemedicine and chronic care management, many parties have a high acceptance of the introduction of digital technology in the medical treatment and health field. Therefore, with the rapid popularization of smartphones and the Mobile Internet in the 2010s, Digital Therapeutics, this new thing, was firstly brewing and sprouting in the United States. Researchers improved clinical treatment by taking advantage of advanced technology or equipment, from which two distinct types of Digital Therapeutics were derived. The first is the therapeutics that extends the value of traditional drug therapy, for example, by providing medication adherence management and personalized treatment recommendations through companion software to help patients manage their conditions, including informing about the time of taking the drug and dose. The second is the therapeutics that replaces traditional medicine, such as delivering sensory stimulation through a tablet computer to

treat insomnia or depression.

The huge chronic disease market is one of the reasons why Digital Therapeutics was recognized at the time. The United States has the world's largest market for chronic disease management. In 2014, 147 million adults in the United States had chronic diseases, and more than 40% of adults had two or more chronic diseases. Of these, more than 30 million suffered from diabetes, the world's fastest growing chronic disease. The American Diabetes Association (ADA) estimated that the US diabetes-related market reached 327 billion dollars in 2017. A large number of medical research results have demonstrated that chronic diseases such as hypertension, diabetes, fatty liver, obesity, and cardiovascular disease have a strong correlation with the lifestyle of patients. These diseases cannot be controlled by drugs alone and the best treatment effect can be achieved by medication on the basis of change and avoidance of patients' bad lifestyle. However, even in the United States, where out-of-hospital management is more developed, its medical treatment and health system is not designed for continuous care of patients with chronic diseases, and people can only perform self-chronic disease management under limited guidance. Pharmaceutical enterprises need a way to improve patient medication adherence for continuous sales of drugs; in order to reduce potential compensation, insurance companies need a way to continuously and stably help patients control their conditions; doctors need a way to help them effectively improve work efficiency and provide more accurate and effective management means; and patients need a way to get healthy. Such common expectation has led to the initial development of Digital Therapeutics in the United States - Digital Therapeutics can track and collect health data, provide operable feedback and continuous health supervision, provide personalized health opinions to patients, and reduce costs.

In addition to chronic disease management, the decisive factor in the recognition of Digital Therapeutics in the United States comes from the industry expectation that it can effectively alleviate the long-standing drug abuse situation in the United States. Digital Therapeutics has significant efficacy in coping with behaviorally mediated conditions that are not well addressed by existing drug therapy (e.g., depression, post-traumatic stress disorder, smoking cessation, type 2 diabetes, and insomnia). For these conditions, traditional drug therapy is not very useful, but can easily cause drug addiction. Opiates addiction, which afflicts the United States, is one of the drawbacks of drug therapy. Opiates analgesics, mainly composed of opium poppy extracts, are the trigger for the most serious drug abuse crisis in the United States today. The number of deaths due to opiates abuse is increasing extremely rapidly year by year. According to the Centers for Disease Control and Prevention (CDC), the number of fatal persons caused by drug abuse in the United States in 2016 was 63,600, of which 19,400 were caused by smoking non-methadone synthetic opiates materials (including fentanyl substances, meperidine and tramadol, but mainly fentanyl substances). In 2017, the number of fatal persons caused by drug abuse is 70,200, of which 28,500 were caused by smoking non-methadone synthetic opiates materials. In 2018, the number of fatal persons caused by drug abuse is 60,800, of which more than 30,000 were caused by smoking non-methadone synthetic opiates materials. Meanwhile, approximately 20 million patients in the United States suffer from alcohol- or other non-drug-related substance use disorders (SUDs), causing more than 700 billion dollars of annual losses

in medical treatment costs, crime, productivity, etc., and endless suffering to families and society. Digital Therapeutics, including mobile applications, enables patients to have convenient access to treatment, effectively improves patient participation, and can enhance the quality control of therapeutics. Admittedly, Digital Therapeutics cannot directly replace drug intervention and does not have the effect of placebo, which is only a beneficial supplement to traditional therapeutics. However, for behaviorally mediated patients, behavioral changes may be more significant and have fewer side effects than antidepressants. It can also be effective in enhancing patients' medication adherence. Meanwhile, Digital Therapeutics combining software and hardware can track the medication status of patients with mental disorders. Based on the real-time monitoring and feedback of the sensor, the medical institution or guardian can know whether the patients take the drug on time - such patients often have low medication adherence, and it is difficult for the medical institution or guardian to effectively track and monitor their medication status.

Based on this, a number of digital therapeutics enterprises have been gradually established and grown up. Those enterprises have made a lot of contributions to the early exploration of Digital Therapeutics. As early as the period 2010-2017, Welldoc, Voluntis and Propeller Health received FDA approval for several medical devices. Such devices either combined with drugs and sensors, or achieved chronic disease management through software. In today's definition, these products are actually in the scope of Digital Therapeutics. However, because the definition and cognition of Digital Therapeutics had not been unified at that time, it did not draw too much public attention.

2017 is a critical year for Digital Therapeutics. Digital Therapeutics has attracted industry-wide attention through two major events.

In September 2017, Pear Therapeutics' ReSET for substance abuse and alcohol abuse disorder was approved by the US Food and Drug Administration (FDA) in the form of De Novo, and gained 510(k) authentication at the end of 2018. This is the first Digital Therapeutics prescribed by the doctor, which uploads, digitizes, and standardizes face-to-face therapeutic regimens for the pain point that the treatment of drug addiction patients is difficult to reach by making use of cognitive behavior therapy. As a supplementary means to emergency management, it applies to patients aged 18 years and older undergoing outpatient treatment under the supervision of clinicians. ReSET has demonstrated its role in improving withdrawal effect and patient survival through clinical trials. Due to the particularity of De Novo, ReSET has attracted strong interest in the industry. This novel therapeutics in which patients can take prescriptions and download APP for disease treatment according to physician requirements subverted the public's perception of disease treatment and therefore gained high media attention and was intensively reported. Because it has evidence-based medicine evidence, APP will also become a drug form. Combined with traditional drugs, it will bring more efficient and popular treatment and will be gradually recognized.

In October 2017, Digital Therapeutics Alliance (DTA) was established. The founding members of Digital Therapeutics Alliance include four enterprises, Akili Interactive, Propeller Health, Voluntis, and WellDoc, and quickly included the main digital therapeutics enterprises afterwards. In 2018, Digital Therapeutics

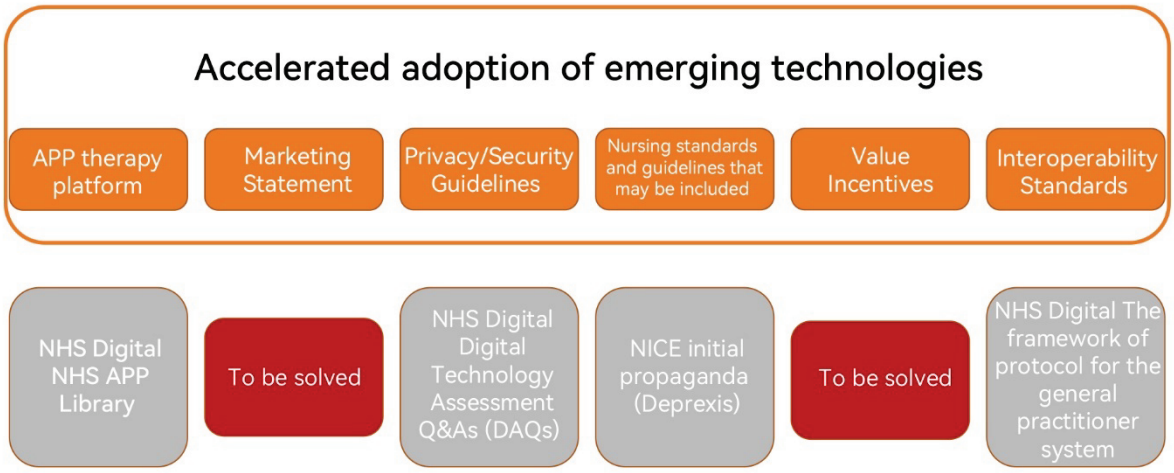
Alliance issued *Digital Therapeutics Industry Report 2018*, which firstly gave clear definition of Digital Therapeutics, and formulated the core principles and best practices relating to design, manufacturing, clinical validation, and supervision. Since its members are all major enterprises in the digital therapeutics industry at that time, these definitions, principles, and guidelines basically became the default industry standards. This also became the catalyst for the development of digital therapeutics industry and played a key role in promoting the great development of Digital Therapeutics in the future.

2.1.2. Europe

Europe has been keeping a close watch on the development of Digital Therapeutics in the United States. However, there is currently no uniform rule for Digital Therapeutics across the European Union. Each country has made its own explorations based on their own frameworks. Among them, the UK and Germany are the faster-paced countries - the former plays the role of enlightener of Digital Therapeutics in Europe, and the latter establishes the first rapid approval process specifically for Digital Therapeutics in Europe and even the world.

The National Health Service (NHS) has been a model for public health systems worldwide. In the application of new technologies, the NHS has always been tolerant and positive, not inferior to the FDA. For example, the NHS launched the National Programme for Health Information Technology as early as 2002. The Programme aims to allow all hospitals to use the software system developed by this project within eight years and promote the level of medical system informatization. It was under the stimulation of the NHS that the United States carried out similar actions.

The NHS has conducted an internal assessment of the resources needed to fast-track Digital Therapeutics in the UK



The NHS has early recognized the potential of Digital Therapeutics in the future. As early as 2018, the NHS hoped to build a friendlier environment for Digital Therapeutics in the UK that can help these clinically validated medical APPs succeed. The NHS believed that for the quick promotion of Digital

Therapeutics, it is necessary to make corresponding preparations on APP comprehensive processing platforms, compliant marketing statements, privacy and security guidelines, medical guidelines that may be included, value-based incentives, and interoperability standards. Obviously, the NHS's understanding of Digital Therapeutics is relatively comprehensive. According to the NHS's self-assessment at the time, apart from the blank in compliant marketing statements and value-based incentives, the NHS was somewhat prepared at the time in several other aspects. For example, the NHS rebuilt the NHS Apps Library in April 2017 and provided corresponding assessment means through NHS's NICE (National Institute for Clinical Excellence) and NHS Digital, which is specifically responsible for guiding and supervising digital health care activities, including privacy, security, clinical and interoperability. Any APPs that pass the assessment will be included in the NHS Apps Library. In fact, the NHS has launched NHS Health Apps Library as early as 2013. However, the NHS closed this platform in 2015 after some studies pointed out that the supervision at that time existed in name only and 28% of APPs had privacy and security problems, and even individual APPs transmitted personal identification data[11]. The NHS, which has learned lessons, particularly emphasizes the assessment of Digital Therapeutics in various ways. Based on comprehensive consideration, the NHS hopes to achieve the goal that "studying Digital Therapeutics in the UK becomes easier" through enhancement in five aspects: Firstly, simplify the initiation and implementation of study programs; Secondly, establish a pre-contracted research network for Digital Therapeutics; Thirdly, establish prescription APP platform and third-party research APP so that patients can contribute their data; Fourthly, introduce standard-compliant independent research teams to produce high-quality research contents; Fifthly, quickly import into usual care.

This shows that the United Kingdom has a deeper understanding of Digital Therapeutics and has developed corresponding promotion measures according to its own actual situation. As the enlightener of European Digital Therapeutics in fact, the United States also laid the foundation for other European countries to understand and accept Digital Therapeutics.

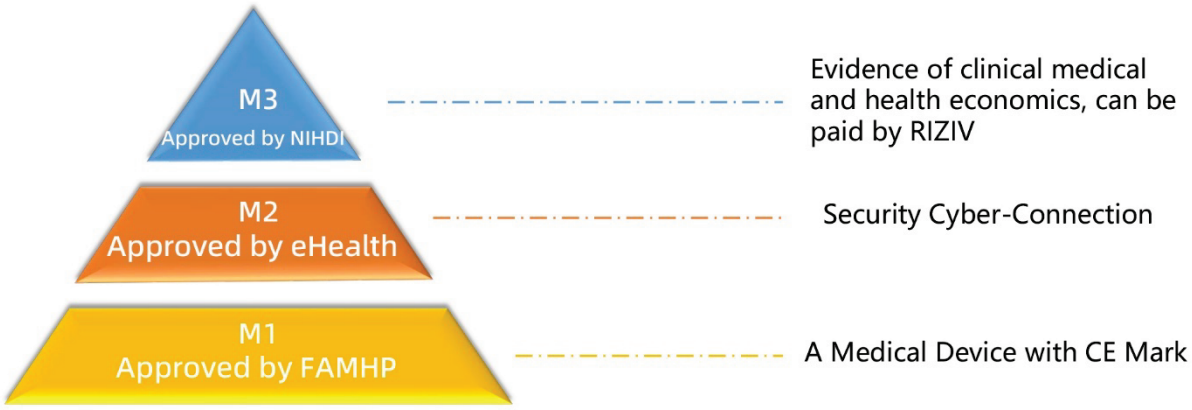
Belgium also follow this field for years—for its part, presented the mHealthBelgium in late 2018, which was set up based on action item 19 of the federal e-health roadmap 2.0. The mHealthBelgium went live for the first time on January 25, 2019. This unique platform centralises all relevant and required information on mobile apps for patients, healthcare professionals and healthcare institutions. The information is related to CE marking, data protection, communication security, interoperability with other IT systems and the way in which the app is financed. This platform is managed by beMedTech (sector federation for industry of medical technologies) and Agoria (sector federation of technological industry), in close cooperation with three national authorities.

It consists of a validation pyramid with three levels. In this 'pyramid', medical Apps enter at the lower level, M1, and could be upgraded via M2 to the top level, M3. mHealthBelgium is an initiative of the

[11] Wicks, P., Chiauzzi, E. 'Trust but verify' – five approaches to ensure safe medical apps. BMC Med 13, 205 (2015). https://doi.org/10.1186/s12916-015-0451-z

Belgian Federal Government. Multiple stakeholders are involved.

Belgium's Digital Therapeutics validation pyramid structure



The M1 level is very basic, which only requires CE declaration. Approval is granted by the competent authority, the FAMHP (Federal Agency for Medicines and Health Products), which approves matters relating to the quality, safety and efficacy of medicines and health products (including medical devices).

The M2 level, the next one, sets requirements of data security and privacy related to internet connectivity for the app, which are approved by the official eHealth platform. The objective of this federal government agency is to promote and support the provision of well-organised and interoperable electronic services and data exchange between all healthcare stakeholders, and to provide guarantees in the areas of data security and data privacy, also respecting the confidentiality of healthcare professionals.

The M3 grade is the most demanding grade, which requires App-related clinical medical or health economics evidence, in order to obtain the mandatory Belgian Health Insurance Fund RIZIV (Rijksinstituut voor ziekte en invaliditeitsverzekering). This level is mainly approved by the NIHDI (National Institute for Health and Disability Insurance), which is responsible for payment for medicines and medical devices.

However, Germany has come to the top in the specific measures promoted by Digital Therapeutics and a special rapid approval process has been established for Digital Therapeutics starting from the top-level design. Firstly, in terms of legislation, The Federal Ministry of Health of German (German: Bundesministerium für Gesundheit, abbreviated BMG,) started to push for legislation in 2018 to achieve digital transformation of German health system. After 18 months of effort, the German *Digital Health Care Act* (DVG, Digitale-Versorgung-Gesetz) came into force on December 19, 2019. DVG became the legal basis of German digital therapeutics, marking Germany will include patients' "prescription App" (namely digital therapeutics) in the medical and healthcare system. In this way, 73 million applicants of statutory health insurance in Germany can pay for digital therapeutics through

the statutory medical insurance. These prescription apps are called as DiGA (abbreviation of "Digitale Gesundheitsanwendungen" in German, meaning digital health applications) in Germany. In order to be more in line with the characteristics of DiGA itself, the German Federal Ministry of Health specified the application process, DiGA requirements and DiGA catalogue in the supplementary legal regulation *Regulations on Digital Hygiene Applications* (Digitale-Gesundheitsanwendungen-Verordnung, abbreviated as DiGAV).

The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, abbreviated as BfArM), a division of the Federal Ministry of Health of German that undertakes tasks such as drug licensing and safety improvement, testing and risk assessment of medical devices, as well as monitoring of narcotic drugs and legal transport and sales in stupefacient, provides corresponding guidance for DiGA approval in accordance with the provisions of the *Social Code - Book V - Statutory Health Insurance*. BfArM specially designed the expedited approval procedure for DiGA and standardized the details of this procedure. Once the corresponding software application is approved by BfArM, becomes a legal DiGA and is included in the DiGA catalogue, this DiGA can be prescribed by health insurance certified physicians for patients with indications and reimbursed by health insurance.

This initiative makes Germany the first country and region to provide specialized expedited approval for Digital Therapeutics, and also provides a valuable experience reference for other countries and regions. EU member states, which are building a common framework for digitization (including France, which has clearly indicated that it would learn from German measures), are also paying high attention and will promote the promulgation and implementation of future corresponding policies for Digital Therapeutics.

2.1.3. Japan

The promotion of Digital Therapeutics in Japan mainly relies on pharmaceutical enterprises. Before 2012, Japan had been the second largest pharmaceutical market in the world. Even today, Japan is still the third largest pharmaceutical market after the United States and China. It owns very developed pharmaceutical industry and a number of global pharmaceutical enterprises in the front rank. Due to policy encouragement, the Japanese pharmaceutical industry has attached importance to R&D in recent decades and has achieved great success, and some enterprises have even become the top 50 in the world by relying on only one or two best-selling varieties. However, there is still a gap between these relatively young pharmaceutical giants and long-established ones in the accumulation of product lines. With passage of time, patents on their best-selling products are about to expire, and their sales and profits are declining rapidly. Digital Therapeutics can help extend the patent term of best-selling drugs and thus increase the source of revenue. The FDA's 505-B of the United States, for example, allows pharmaceutical companies to obtain the extension of patent term through the redevelopment of existing drugs, giving them an incentive to invest in R&D and improve their products. The FDA has approved the combined use of drugs and Digital Therapeutics to supplement and

strengthen traditional therapeutics as a way to obtain the extensions of patent terms. This is undoubtedly a savior for Japan, which is about to face the patent cliff. Besides, Digital Therapeutics can help enhance patients' stickiness of medication. Therefore, Japan's pharmaceutical enterprises cooperated with digital therapeutics enterprises a lot. In January 2019, Otsuka Pharmaceutical and Click Therapeutics cooperated to develop the commercially available Digital Therapeutics for major depressive disorders. This is also the first collaboration between a Digital Therapeutics enterprise and a large pharmaceutical enterprise, which is a huge opportunity for both industries. Subsequently, Japan's pharmaceutical giants such as Shionogi and Takeda Pharmaceutical began to combine their products with Digital Therapeutics. Takeda Pharmaceutical also developed myPKFiT, the Digital Therapeutics for hemophilia - interestingly, myPKFiT was not developed locally in Japan, but from Baishen Baxalta US, a subsidiary acquired by Takeda Pharmaceutical.

On October 18, 2019, Aillis, Astellas Pharma, Digital Garage, Mitsubishi Tanabe, Shionogi, SUSMED and Teijin Pharma co-founded the Japan Digital Therapeutics Consortium (JDTx). JDTx hopes to focus on evidence-based medicine evidence for Digital Therapeutics, based on which the medical value of Digital Therapeutics can be improved. In order to achieve this goal, industry giants and startups in the pharmaceutical, medical device, and IT fields should work together to promote the Digital Therapeutics industry and overcome current challenges, such as R&D, policy development, and channels. It deserves to be mentioned that there are a total of 4 in 7 founding enterprises are pharmaceutical enterprises, which shows the huge role of pharmaceutical enterprises in promoting the development of Digital Therapeutics in Japan. In August 2020, CureApp SC's nicotine addiction treatment application and carbon monoxide detector (CureApp SC) in Japan was approved by Ministry of Health, Labor and Welfare for manufacturing and sales. This is considered to be the first officially prescribed Digital Therapeutics in Asia and the world's first Digital Therapeutics approved by the national regulatory authority as an effective treatment for nicotine addiction. Nevertheless, the Japanese Society for the Promotion of Digital Therapeutics believes that in reference to the situation in Germany, breakthroughs in the rapid approval and pricing system are still needed for Digital Therapeutics to be further promoted in Japan.

2.1.4. South Korea

South Korea, which has a place in the field of high and new technology, is also correspondingly prepared for Digital Therapeutics. In July 2019, the Ministry of Food and Drug Safety (MFDS) of South Korea approved a clinical trial for Nunaps' Nunap Vision Digital Therapeutics. The early conceptual validation of this Therapeutics has been demonstrated, followed by the opening of multi-center, double-blind, randomized, and placebo-controlled pivotal clinical trials, to further demonstrate the role of this Digital Therapeutics in improving visual impairment after brain injury. This is also the first clinical trial of Digital Therapeutics in South Korea.

In October 2020, MFDS issued the *Guideline on Review and Approval of Digital Therapeutics (For Industry)*, which aims to guide the scope and standards of Digital Therapeutics review and approval

in South Korea for the Digital Therapeutics industry. However, this Guideline is the "Guideline" for industry, not compulsory.

2.2. Global policy promotion of Digital Therapeutics

Not only in China, the medical treatment and health industry belongs to the strongly regulated industry worldwide. Therefore, policies are often essential for the development of the medical treatment and health industry. Policies also play an extremely important role in driving the development process of Digital Therapeutics.

To date, Digital Therapeutics is in the early stages of development and its regulatory framework is still vague. However, regardless of the definition, one of the important characteristics of Digital Therapeutics is "software". As technology continues to advance into all aspects of medical treatment and health, software has become an important part of all medical treatment and health products and is widely integrated into digital platforms serving medical and non-medical purposes. According to different purposes, the software related to medical devices can be divided into three categories: the software to manufacture or maintain medical devices, Software in a Medical Device (SiMD) and Software as a Medical Device (SaMD). Given the unique functionality of Software Medical Devices beyond traditional Hardware Medical Devices, regulators worldwide recognize the need to integrate common frameworks and principles for Software Medical Devices to enable all stakeholders, including regulators, to promote safety innovations and protect patient safety. This responsibility is primarily vested in the International Medical Device Regulators Forum (IMDRF), a voluntary group of global medical device regulators, which is responsible for developing internationally agreed documents related to various topics affecting medical devices to achieve the unified regulation of global medical devices. In 2013, IMDRF established the Software Medical Device Working Group to agree on criteria for critical definitions, risk classification frameworks, quality management systems, and clinical assessments. This also sweeps away the obstacle for Digital Therapeutics to be approved.

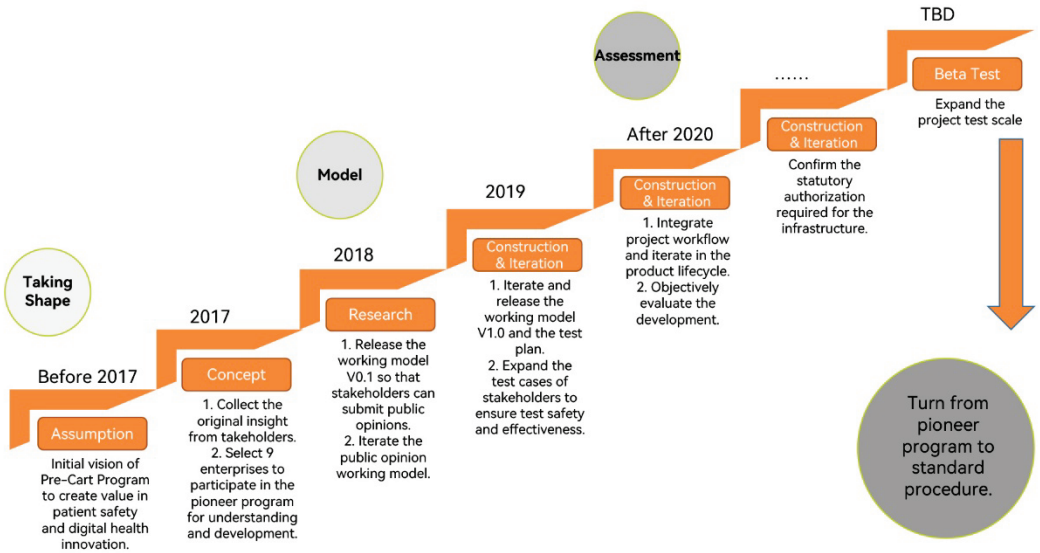
Despite this, most medical device regulators still approve Software Medical Devices represented by Digital Therapeutics in the way of traditional medical devices at the early stage. This has led some to believe that digital technologies should not require evidence-based medicine evidence as new drugs do. Since the process of evidence-based medicine is slow, and it is difficult to keep pace with the dynamic nature of digital technology, it may throttle technical development and payment. However, it is also believed that, digital therapeutics should not be excluded from the standards required by other therapeutics. Regulators still should carry out objective evidence-based assessment of digital therapeutics so as to set standards for the development of digital therapeutics in the future[12]. In fact, both views have respective reasons. For example, AI algorithm in the field of medical treatment and

[12] Greaves F, Joshi I, Campbell M, Roberts S, Patel N, Powell J. What is an appropriate level of evidence for a digital health intervention? Lancet. 2019 Dec 22;392(10165):2665-2667. doi: 10.1016/S0140-6736(18)33129-5. Epub 2018 Dec 10. Erratum in: Lancet. 2019 Dec 22;392(10165):e18. PMID: 30545779.

health mainly includes "fixed algorithm" and "adaptive learning update dynamic algorithm". The latter has self-learning capacity, and can achieve a certain degree of self-learning and update. According to traditional change examination and approval mode, these software and medical devices with self-learning update capacity may require pre-marketing investigation for every adaptive evolution. In view of the fast update frequency of software industry, such traditional examination and approval method is obviously not suitable for software and medical devices including digital therapeutics.

In July 2017, Center for Devices and Radiological Health (CDRH) subordinate to FDA issued the Digital Health Innovation Action Plan, proposing new measures to supervise medical software. The release of this Plan aims to promote the continuous innovation of digital health. In August 2017, FDA started to launch the Pre-Cert for Software Pilot Program, and invited the industry to participate in cooperative development. This program aims to adjust the examination and approval process for the feature of fast software update, and the selected companies are allowed to make small changes to equipment rather than submitting the revise application every time. Besides, FDA will ensure other aspects of the regulatory framework such as new software verification tools) are flexible enough to meet the unique attribute of this booming field and ensure these new technologies can reach safety and effectiveness standards.

Digital Health Innovation Action Plan by FDA



Through the screening for one month, 9 enterprises finally stood out from over 100 candidates, which will cooperate with FDA to complete the development of the Pre-Cert for Software Pilot Program. The 9 enterprises include Apple, Fitbit, Johnson and Johnson, Pear Therapeutics, Phosphorus, Roche Group, Samsung, Tiderpool and Verily. Pear Therapeutics is the representative of digital therapeutics, and its ReSET digital therapeutics obtained the certification of De Novo by FDA in September. Through the R&D for one year, the Pre-Cert for Software Pilot Program entered the test phase in 2019, and it

was promoted in accordance with the scheduled progress.

At the end of 2019, COVID-19 spread all over the world. At the beginning of the pandemic, most regions launched isolation and social distance measures in order to prevent further spread of the pandemic. However, these measures had significant impacts on patients with chronic diseases and mental health problems. Considering the increasing possibility of cyclical impacts caused by the pandemic, United States Department of Health and Human Services (HHS) and FDA jointly released *Enforcement Policy for Digital Health Devices For Treating Psychiatric Disorders During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency* in April 2020. This policy temporally gave up the requirements for low-risk software tools related to mental health, such as the requirement for report correction and deletion and the requirement for registration and marketing. FDA specifies that the approval and registration may be cancelled for two kinds of digital therapeutics: the first one is "digital behavioral therapeutics devices for mental health diseases and other digital therapeutics devices"; the second one is "low-risk comprehensive healthcare and digital health products for mental health and mental state treatment". Of course, this does not mean such low-risk digital therapeutics can be released at will. They still need to pass the quality assessment, including software verification and network security. FDA also requires enterprises to label clearly so that users could easily distinguish the products officially passing the approval and the products only passing the emergency approval. Meanwhile, enterprises also should clearly label product indications, applicable age and description of clinical trials. If a product includes the content excluded in FDA guideline, it also should be labeled.

For the patients affected by the pandemic, digital therapeutics is a piece of good news in terms of the efficacy of mental illness. Due to the impacts of the pandemic, the huge stress caused by the inability to visit regularly, long-time isolation or social distance keeping, and great uncertainty about the future makes people with mental health problems and patients with chronic conditions deteriorated rapidly. Most patients with mental disease need immediate treatment, which will undoubtedly make the already overburdened health system of the United States unable to bear the heavy burden. In addition, for the elderly patients, visiting medical institutions during the epidemic is very risky. In such a special period, digital therapeutics has several unique advantages. Firstly, digital therapeutics can achieve remote access for inquiry or treatment to reduce unnecessary visits of hospitals and clinics during the pandemic. Secondly, digital therapeutics can be customized for patients according to their time and physical space. It is also easy to be expanded, and can be visited very conveniently via mobile phone or tablet PC. Thirdly, as a serious diagnosis and treatment means verified clinically, digital therapeutics can acquire true and usable patient data to optimize patients' results and prevent exacerbation, thereby reducing hospitalization. Besides, it can provide progress update for patients, nursing staff and clinicians so as to achieve intelligent nursing management and clinical decision optimization. For example, it can automatically measure drug consumption, and send such information to drugstores to provide personalized door-to-door services, which avoids patients' visits of drugstores during the pandemic. Fourthly, compared with traditional therapeutics, the price of digital therapeutics is cheaper, and the economic burden of patients is thud reduced. In addition, it can expand the scope of treatment

without expansion of medical resources, which lowers the cost in a disguised form.

Within one month upon the release of the policy, 3 kinds of digital therapeutics passed the emergency approval, including digital therapeutics of Akili Interactive Labs for attention deficit hyperactivity disorder in children, digital therapeutics of Livongo for diabetes management, and digital therapeutics of Pear Therapeutics for schizophrenia.

An untended willow grows. Although this policy is not customized for digital therapeutics, it has greatly promoted digital therapeutics. Digital therapeutics enterprises can obtain valuable data and user experience feedback from users' use process so that they can improve their products and clinical trials. This will greatly facilitate the final approval. For example, Endeavor digital therapeutics of Akili Interactive Labs has passed the emergency approval and is available for the public free of charge, which has had a significant effect on its certification – Endeavor digital therapeutics was approved in the manner of De Novo only two months later. For patients and medical institutions, they can experience the actual effect of digital therapeutics in person, dispel worries and persuade payers to pay for digital therapeutics, thereby laying a foundation for further promotion of digital therapeutics in the future. Digital therapeutics in the United States is mostly paid by commercial insurers and not covered by health insurance or the medicaid program of most states. The mainstream concept and worries about the efficacy are the main reasons for preventing payers from paying for digital therapeutics. Prior to the outbreak of the pandemic, digital therapeutics had been trying to solve the payment problem by binding with drug and medical instrument companies. The special circumstances during the pandemic made more have to choose digital therapeutics. This is also an opportunity for breaking the concept and displaying the efficacy of digital therapeutics.

In September 2020, FDA set up Digital Health Center of Excellence (DHCoE) in CDRH, further promoting its supervision of digital health field and the development of this field. DHCoE will coordinate digital health work of FDA. The digital health field involved covers software and medical device (SaMD), AI and machine learning (AI/ML) in SaMD, network security, medical device function and application including mobile medical application, medical informatization, medical device database, medical device interoperability, telemedicine and wireless medical device. DHCoE hopes to enable digital health stakeholders to empower healthcare through promoting responsible and high quality digital health innovation, including policy and technology support and training for digital health, network security for medical devices, AI and machine learning, progress of supervision science, regulatory review support and coordination, advanced manufacturing, real world evidence and advanced clinical research, supervision innovation and strategic partners. DHCoE supports and encourages developers (including those who just contact the healthcare field) to further transform digits into tools benefiting consumers. This is achieved through extensive services. These services cover developing an easily accessible knowledge center and building new strategic partnerships with the industry. Moreover, DHCoE is also creating a network of digital health experts to share information and professional knowledge with FDA. For instance, DHCoE plans to reconstruct its supervision for software and medical devices through the Pre-Cert for Software Pilot Program and other ways, and

explores how to utilize the unique advantages of AI and machine learning in SaMD to adjust FDA's supervision of digital health technology. DHCoE will also provide continuous definition for the policy and supervision, and make efforts on international coordination of digital health supervision. For digital health innovators such as digital therapeutics, this is undoubtedly a piece of good news.

Like the United States, Europe still has no specific policy on digital therapeutics at the EU level. Medical Device Regulations (MDR) (EU) 2017/745 passed in May 2017 did not take effect till May 26, 2021. The Regulations on clinical research and marketing of medical devices have replaced the old version of Medical Device Directive (MDD) (93/42/EEC) and Active Implanted Medical Device Directive (AIMDD) (90/385/EEC). For digital therapeutics, European Medicines Agency (EMA) and European Commission (EC) are exploring the overall solution.

EU member states tried to stimulate the promotion of digital health technologies including digital therapeutics through formulating various policies. From June 2018, NICE was entrusted to lead and complete *Evidence Standards Framework for Digital Health Technologies*. This Framework is intended for technical developers to provide information for their evidence development plans, and for decision makers who are considering debugging DHT. This Framework mainly describes evidence standards that digital health technologies including digital therapeutics should provide or develop so as to prove the value in the British health and social nursing system. In addition to this, Public Health England (PHE) also created practice online guidelines to help technical developers evaluate their products. Apart from the United Kingdom, Germany also started to drive legislation in 2018 to achieve digital transformation of German health system. After 18 months of effort, the German *Digital Health Care Act* (DVG, Digitale-Versorgung-Gesetz) came into force on December 19, 2019. DVG became the legal basis of German digital therapeutics, marking Germany includes the "prescription App" (namely digital therapeutics) for patients in the medical and healthcare system. In this way, 73 million applicants of statutory health insurance in Germany can pay for digital therapeutics through the statutory medical insurance.

In most cases, digital therapeutics has certain requirements for network. Therefore, policies on network and data security have also had significant impacts on digital therapeutics in recent years. In this field, Europe is leading in the world. The United States passed the famous *Health Insurance Portability and Accountability Act* (HIPAA as early as 1996, which has formed certain restraints for data security in the medical and healthcare field. However, a uniform data protection law across the country has not been formed, and there are still some edge zones. The root is that high-tech giants gather in the United States and have strong competitiveness around the world, the United States tended to focus on ensuring the development of digital economy and the order of free market competitions. By contrast, Due to the historical reason and other reasons, the EU regards data privacy as the basic right of individuals and highly protects the security of personal information. Its *Data Protection Directive* (DPD) was released in 1995, earlier than the release time of HIPAA. In May 2018, *General Data Protection Regulation* (GPDR) used to replace DPD was officially enforced in the EU. This is also the strictest regulation for data security and privacy around the world. For example, GDPR stipulates that

if an enterprise fails to undertake the specific responsibility of data controller and processor, it may be fined EUR 10 million or 2% of the annual turnover. In the event of security vulnerabilities during data processing, the fine may be doubled. GDPR also has strict regulations on cross-border data transmission. Unless relevant countries and regions obtain the recognition of the EU in terms of data protection mechanisms and enter the “white list” of GDPR, any enterprise cannot transmit data beyond the EU before safety measures recognized by the EU are taken. Besides, GDPR also has extraterritorial jurisdiction. Even if an enterprise is outside the territory of the EU, as long as it provides commodities or services in the EU and even just uses cookies and other programs to track browsing records of EU citizens and residents on websites, it will be governed by GDPR.

In terms of establishing personal information protection systems, Japan drew on the American concept of privacy right and the legislative model experience of the EU and established a personal information protection system with national characteristics. Firstly, Japan established basic principles of personal information protection based on the “the fundamental law”. As early as 2003, Japan issued the *Act on the Protection of Personal Information*, and revised it in 2015, further clarifying basic principles of personal information protection. For the protection and use of medical data, the *Act on the Protection of Personal Information* has several major regulations: first, the major purpose should be to promote the development and utilization of information and data; second, "personal information" (sensitive information) shall be noticed during regulating medical information; third, the circulation of personal information shall be noticed. It is not applicable to “opt-out” mode (after the data processor informs the person of the regulations or makes them in a state easily accessible to the person in advance, and files a declaration to the Personal Information Commission, the data of this person can be provided to a third person); fourth, confirmation, recording and preservation obligations during accepting or providing "personal Information which shall be noticed". Secondly, in order to make data collection and provision easy based on the characteristics of industry development under the precondition of protecting the privacy of medical data, Japan formulated “a specialized law” - *Act on the Foundation of Next Generation Healthcare* as an important supplement of the “fundamental law”. The *Act on the Foundation of Next Generation Healthcare* was issued in May 2017 and enforced in May 2018. While supplementing the principal provisions of the *Act on the Protection of Personal Information*, the Act details circulation rules and protection mechanisms for healthcare data, and designs the system of “anonymous processing + accreditation” and supporting measures: first, it sets up the anonymous processing system and allows the circulation of medical information processed anonymously; second, it establishes the national accreditation system and adds the anonymous processors of medical information in the white list; third, it develops a special regulation method and allows the accredited makers to adopt the “opt-out” mode; fourth, it maintains patients' rights through written notice and ensuring the right of refusal. Through the double regulation framework of “fundamental law + specialized law”, Japan emphasizes the balance between application and protection of medical data on the basis of data protection. In the meantime, “the combination of delegating power and strengthening regulation” is achieved through the hierarchical protection mode of “fundamental law”

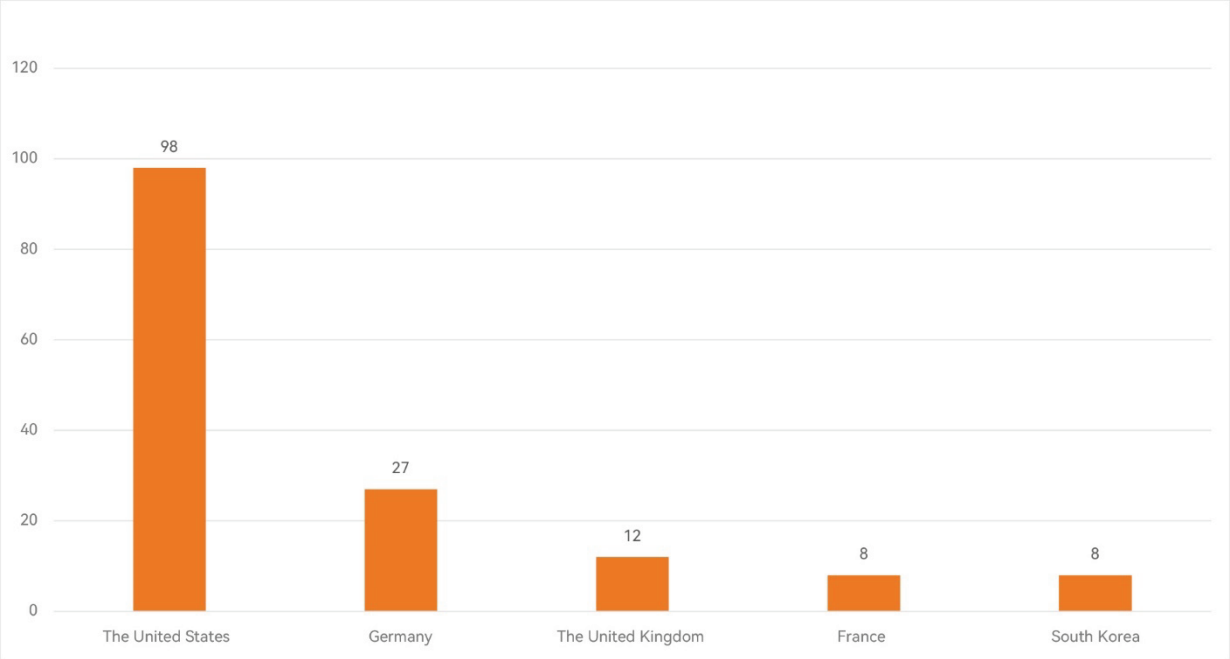
and “specialized law”. [13]

2.3 Global industry clusters for Digital Therapeutics

The development of any industry to a certain stage will often form industrial clusters in specific areas.This is also a distinctive economic organization form in today’s world. Industrial clusters promote the interdependence, mutual cooperation and mutual attraction of enterprise organizations in the region; on the one hand, industrial clusters are conducive to reducing the operating costs of enterprises, including labor costs, development costs and raw material costs, which are conducive to improving the labor productivity and competitiveness of enterprises; on the other hand, the interaction between enterprises in clusters can produce the synergistic effect of "the whole is greater than the sum of the parts", which is ultimately conducive to improving regional competitiveness and promoting regional innovation development.

As an emerging industry, has digital therapeutics formed certain industrial clusters? What factors does digital therapeutics value according to the agglomeration areas? We conducted statistics and analysis of geographical locations of 193 main foreign digital therapeutics enterprises collected in this report. It is necessary to point out that digital therapeutics is a fast-growing industry and is still in the initial stage. Thus, our statistics only covers main and well-known enterprises rather than all enterprises.

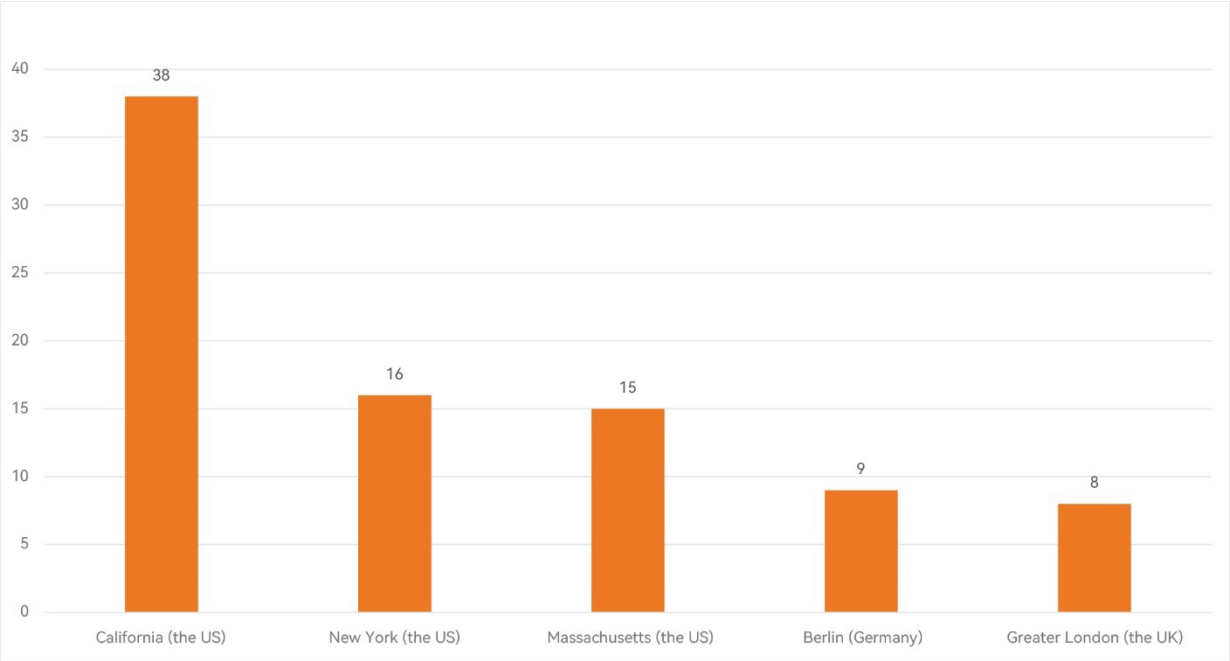
Top 5 Countries and Regions in Terms of Quantities of Foreign Digital Therapeutics Enterprises



[13] Li Huimin, Chen Guang, "On Conflict and Balance Between Data-driven Innovation and Personal Information Protection—A Study of Japan's Medical Data Regulation Experience", [J]. Bulletin of the Chinese Academy of Sciences, 2020,35(9):1143-1151.DOI 10.16418/j.issn.1000-3045.20200522002

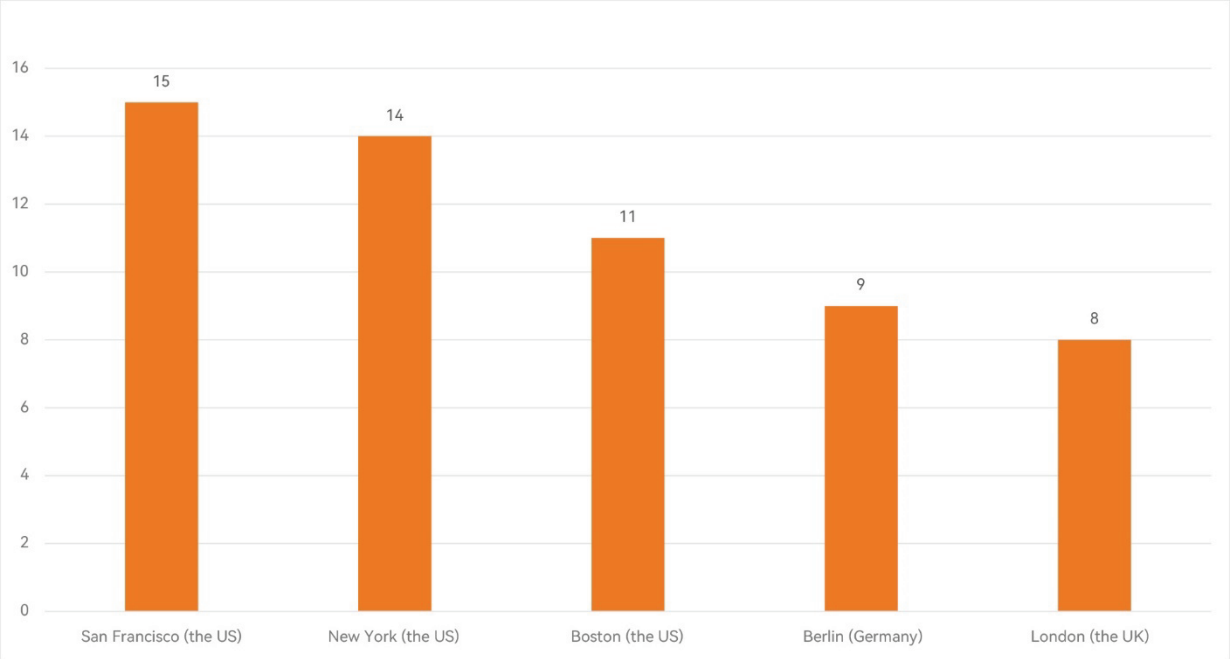
In terms of country and regional distribution, there are 98 digital therapeutics enterprises in the United States, accounting for 50.8% of the 193 foreign enterprises. It ranks top 1 globally. As the place of origin of digital therapeutics, tis result is not surprising. Germany (27 digital therapeutics enterprises) and the United Kingdom (12 digital therapeutics enterprises) are in the second and third places. There are 65 digital therapeutics enterprises across Europe, including the United Kingdom.

Top 5 Regions in Terms of Distribution of Foreign Digital Therapeutics Enterprises



In terms of regions, the number of digital therapeutics enterprises headquartered in California is the largest – there are 38 digital therapeutics enterprises are from California. This also verifies the high correlation of digital therapeutics with internet and software technology. After all, the world famous “Silicon Valley” is located in California. New York and Massachusetts rank the second and the third places, where 16 and 15 digital therapeutics enterprises are headquartered respectively. It is worth mentioning that, the number of digital therapeutics enterprises in the two regions is even more than that in the United Kingdom. The advantage of the United States in digital therapeutics can be seen. There are 9 digital therapeutics enterprises in Berlin, Germany, ranking the fourth place. There are 8 digital therapeutics enterprises in Greater London, the United Kingdom, ranking the fifth place. These regions basically constitute the basic territory of global digital therapeutics.

Top 5 Cities in Terms of Distribution of Foreign Digital Therapeutics Enterprises



Through further detailing, we have found that, there are 15 digital therapeutics enterprises from San Francisco. Because the "Bay Area" in the United States is convenient in transportation, many companies are distributed in cities around San Francisco, which also decentralizes its strength. New York, USA ranked second with 14 digital therapy companies, followed closely by Boston, USA with 11 digital therapy companies Considering that New York and Boston are just across the river from each other, and that industry giants such as Click Therapeutics, Akili Interactive, and Pear Therapeutics are all located in the region, this suggests that the concentration of digital therapeutics industries on the East Coast of the United States is no less than that on the West Coast of the United States.Berlin, Germany, ranks fourth with 9 digital therapeutics companies, while London, UK, ranks fifth with 7 digital therapeutics companies. As the capital cities of both countries, Berlin and London also contain the best of German and British digital therapeutics.

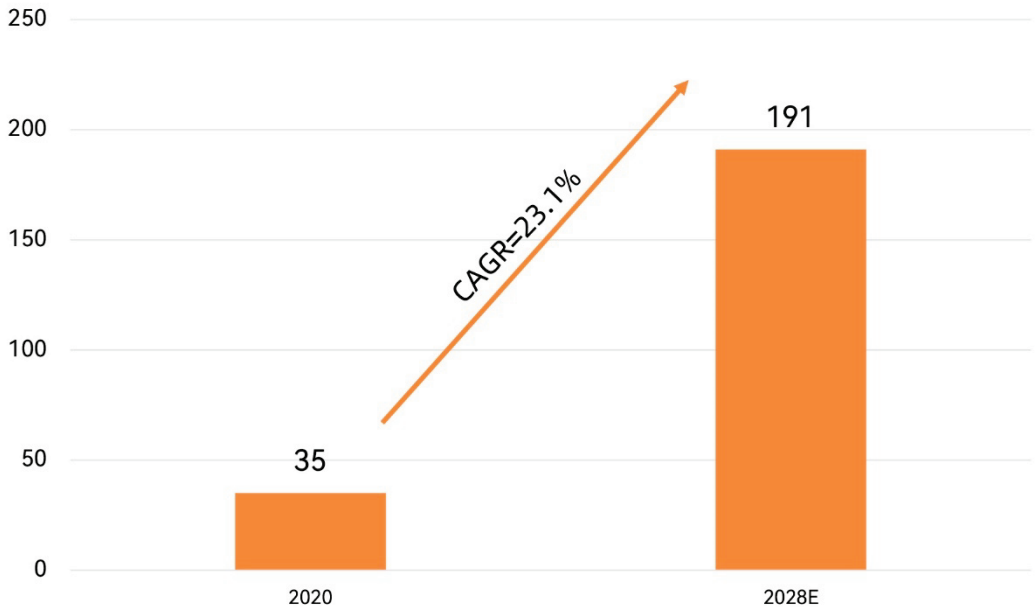
Through the analysis of the global digital therapeutics clusters, it is easy to see that the global concentration of Digital Therapeutics has been formed in national and regional technology centers or financial centers, such as the "San Francisco + Silicon Valley" on the west coast of the United States and the "Boston + New York" on the east coast of the United States, forming features of technology + finance. This shows the highly pro-software, internet and financial nature of the industry - the development and operation of the product itself is highly linked to software and the internet, and further development requires breaking through the constraints of financing and even insurance payments.

2.4 Forecast of global Digital Therapeutics market size

According to the statistics of Global System for Mobile Communication Association (GSMA), 2/3 of population in the world used mobile services in 2021. By 2025, the number of global mobile Internet

users is expected to reach 5 billion. According to the statistics of GSMA, the number of global 5G users broke through 500 million in 2021[14]. As the mobile communication technology develops and Internet popularity increases, the scale of global digital health market has grown rapidly in recent years. At present, the quantity of digital health Apps has exceeded 350,000. A total of 90,000 digital health Apps increased in 2020, and global digital health investment also set the record of USD 24 billion in 2020[15]. According to the data in the *Digital Medical Market Size and Growth Report* issued by Grand View Research, the scale of global digital health market was USD 96.5 billion in 2020, and it is expected to grow at the compound annual rate of growth (CAGR) of 15.1% from 2021 to 2028[16].

Global Digital Therapeutics Market Size (Unit: USD 100 Million)



With the rapid development of digital health market, global Digital Therapeutics (DTx) market size is increasing. In 2020, the scale of global Digital Therapeutics market was USD 3.5 billion, and it is predicted to grow to USD 4.4 billion in 2021. The CAGR will reach 23.1% from 2021 to 2028, and finally the size will reach USD 19.1 billion by 2028.

The growing popularity of mobile Internet, the growing demand for medical cost control, the gradual rise in the incidence of chronic diseases and psychiatric disorders, and the substantial shift in attitudes toward medical intervention software due to the new COVID-19 pandemic, have brought the global

14 GSMA: The Mobile Economy 2021

15 IQVIA: Digital Health Trends 2021

16 Data source: https://www.grandviewresearch.com/industry-analysis/digital-health-market

Digital Therapeutics industry into the fast lane of development due to a confluence of factors. Currently, there is still a lack of overall awareness of Digital Therapeutics in many countries and regions, and coupled with concerns about patient data privacy, the market growth for Digital Therapeutics may be limited. However, in the long term, this is high growth space that is part of an untapped market and will present key profit opportunities for Digital Therapeutics companies.

2.5 Business model of global Digital Therapeutics

The COVID-19 has brought an unprecedented change of people's acceptance for the application of digital technology in the healthcare field. Digital Therapeutics is a new means to improve clinical outcomes, but the commercialization of Digital Therapeutics products is still a large challenge due to the lack of reimbursement ways for payers matching the value of it. Nowadays, people's demand for digital medical solutions is higher than ever before. For both payers and Digital Therapeutics enterprises, it is quite necessary to explore possible payment solutions. There are 5 major Digital Therapeutics business models across the world.

Global Major Digital Therapeutics Business Models

Payment way	Object	Detailed description
Hospital prescription	Healthcare providers	Doctors or other healthcare providers collect fees according to specific services of Digital Therapeutics
Employer's offer	Corporate employers	The Digital Therapeutics is included in the suitable employee health benefit plan which is not covered by the healthcare insurance
Insurance payment	Commercial insurance/healthcare insurance	The Digital Therapeutics policy that can be directly accounted is provided for the insured. /As a special retail prescription product with national drug code, the Digital Therapeutics is included in the directory of health insurance drugs
Pharmaceutical company's offer	Biological medicine companies	The Digital Therapeutics is provided for patients to obtain market opportunities and patient data
Self-payment by users	Patients	The Digital Therapeutics subscription service in the APP is provided for patients, and they can directly pay to subscribe it

Hospital prescription: Doctors give Digital Therapeutics prescriptions for patients, and the fees are covered by the patient's health insurance. For example, the access threshold of prescription Digital Therapeutics is high in the United States, and the strict certification system of FDA provides a strong guarantee for product effectiveness, safety and the accountability system.

Corporate employers: it is suitable for Digital Therapeutics products for chronic diseases that help employers improve employee productivity and reduce insurance costs. Employers should pay fixed

fees monthly for employees joining in the benefit plan. For example, Hello Heart's Digital Therapeutics product for hypertension control supports corporate employers to change the amount paid according to the product effect, and it provides return on investment (ROI) calculation services for employers.

Insurance payment: 1. Insurance companies should pay Digital Therapeutics enterprises monthly and provide corresponding Digital Therapeutics solutions for the insured. The payment amount can also be changed according to the intervention effect. Happify Health adopts this model. 2. Digital Therapeutics products are included in the directory of health insurance and the fees can be reimbursed through health insurance. For example, Pear Therapeutics has signed a contract with MassHealth of Massachusetts. MassHealth will cover Prescribed Digital Therapeutics products reSET and reSET-O of Pear Therapeutics which are used to treat drug addiction and opioid abuse. Hence, Pear Therapeutics became the first Digital Therapeutics supplier cooperating with a state health plan for product reimbursement.

Pharmaceuticals companies: There are two payment ways. First, Digital Therapeutics enterprises provide services or patients for free, and then pharmaceuticals companies pay for data that Digital Therapeutics enterprises collected from patients or services that improve patient adherence/participation. Second, pharmaceuticals companies perform clinical trials on the Digital Therapeutics platform and pay pharmaceutical service fees to Digital Therapeutics suppliers. The digital clinical trial platform uMotif adopts this model.

Patients: Digital Therapeutics products are directly sold to self-paying patients. But in the American market, people are not willing to relevant medical expenses except for medical and health insurance. In the field not covered by health insurance, product subscription fee is 99 cents/month to 10 U.S. dollars/month, further declining consumers' willingness to pay. But this model can shorten the sales cycle and rapidly collect user data, and feedback the data to the product R&D and improvement field, hereby rapidly verifying the effect of Digital Therapeutics products.

In general, the business models of Digital Therapeutics are not either this or that, but can be changed at intervals or combined. Dario Health, the supplier of Digital Therapeutics for chronic disease is taken for example. The software-based D2C model of Dario Health is great. The software accumulated over 8,000 user comments within three years, and the mean score was as high as 4.9 points (full mark: 5 points). It provides service examples and data support for subsequent expansion of corporate employer payment and commercial insurance payment. At present, Dario Health has adopted a mixed business model to enter different target markets. But, it is not easy to make the mixed business model work, and it is required to conquer different types of payers at the same time. Therefore, many enterprises only choose one direction in the beginning and then expand after obtaining the market verification. For example, Hello Heart, a company of Digital Therapeutics for chronic disease, originally cooperated with a large enterprise Ieso Digital Health to focus on access to several clinical commissioning groups in British NHS. Pear Therapeutics entered from the addiction treatment center.

In addition to the expansion of business models, it is also the similar pathway for the increase of indications. Many Digital Therapeutics companies initially concentrate on one certain disease. When

the first product is verified by the market, they will carry out product R&D for multiple diseases. For instance, the initial product of Hello Heart is a hypertension control product, and now it has extended to all diseases in connection with heart health and arrhythmia control, cholesterol control and diabetes control. uMotif started from Parkinson's disease, and now can support clinical trials of over 25 disease fields[17].

At the end of the day, the acceptance level of the existing market should be consulted for the establishment of initial business models. Based on specific circumstances of different countries and regions, payers have different acceptance levels for Digital Therapeutics. For example, Pharmacy Benefit Management (PBM) has played an important role in improving the acceptance level of Digital Therapeutics. In a short term, PBM is likely to be the optimal entry point for Digital Therapeutics reimbursement. Pear Therapeutics is one of the companies which take the lead in reimbursing Prescribed Digital Therapeutics (PDT), and has cooperated with at least three PBM companies, including OptumRx, RemedyOne and Prime Therapeutics. Big Health which provides Sleepio and Daylight Digital Therapeutics for insomnia and anxiety disorder, has created a unique PBM reimbursement strategy together with American drugstore giant - CVS Health.

Attitudes of Main Payers of Digital Therapeutics in the United States

Payer	Attitude to the introduction of Digital Therapeutics products
Managed Care Organizations (MCOS)	Tend to make specific business demands clear first, and then scout the specific Digital Therapeutics solutions out
Pharmacy Benefit Managements (PBM)	Tend to welcome Digital Therapeutics enterprises to offer protocols, but give priority to the diseases with great potential for cost saving.

In addition, employers may become early advocates for Digital Therapeutics after adopting individual pilot programs. The willingness of managed care organizations (MCOs) to cover Digital Therapeutics products remains relatively low until national, real-world evidence of digital therapy products is available. For Digital Therapeutics products that do not make it into MCOs and PBMs, there is still ample opportunity to expand 2B business. After all, corporate employers are increasingly embracing Digital Therapeutics products as a way to improve employees' health and retention benefits, and are particularly interested in digital therapy products in chronic disease areas such as diabetes and mental health.

In addition, although most commercial payers are aware of the definition of Digital Therapeutics products by organizations such as the Digital Therapy Alliance (DTA), in practice they have not yet

[17] https://www.mckinsey.com/industries/life-sciences/our-insights/moving-digital-health-forward-lessons-on-business-building

been able to make a clear distinction between Digital Therapeutics and other digital health products. The lack of effective differentiation and screening mechanisms has left payers with the impression that digital health products are overwhelmingly available, thus clouding their true judgment of the future of Digital Therapeutics products. There is no consistent methodology across commercial payers in the United States on how to assess whether to pay for Digital Therapeutics, and willingness to pay varies. They are more interested in seeing solutions emerge that have both clinical evidence and the ability to reduce healthcare costs and share risks.

Another view in the industry is that similar to small molecule drugs, the R&D cost of Digital Therapeutics is quite high, but the marginal cost of production expansion is low. Therefore, to establish a successful payment relation, Digital Therapeutics innovation enterprises should develop strategies while focusing on R&D. Digital Therapeutics enterprises and their industry partners need to conduct information transfer around key requirements if specific payer types, and work out the optimal strategic pricing model and risk sharing contract so as to enhance payers' willingness to pay. Besides, they must determine in advance that they can prove the economic value of Digital Therapeutics in real work research. Moreover, Digital Therapeutics enterprises should continuously guide payers to adopt a standardized evaluation system, and differentiate the clinically verified Digital Therapeutics from more extensive digital health intervention measures. All these will contribute to opening up commercial channels of Digital Therapeutics and improving the bargaining capacity of products. In general, real world evidence, clinical trial evidence and economic analysis are crucial for the promotion of Digital Therapeutics.

2.6 Investment and financing analysis of global Digital Therapeutics

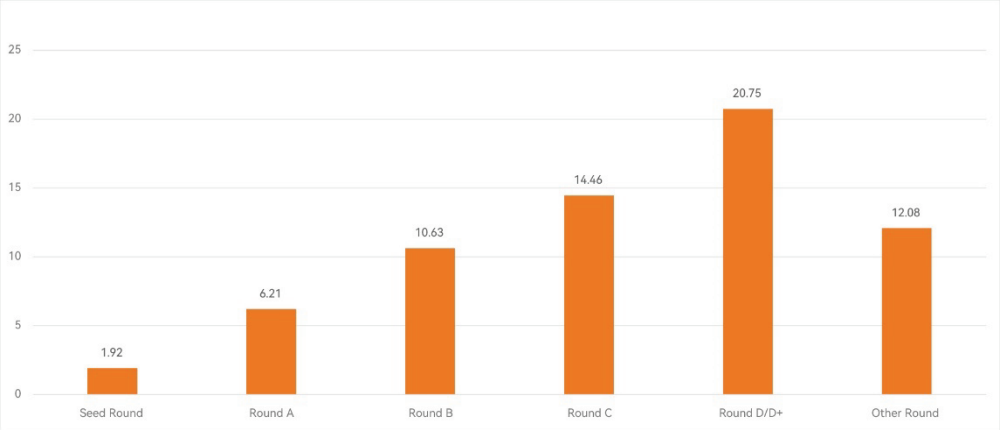
Investment and financing events of medical and healthcare industry have been the focus of the healthcare industry. We regarded the period from January 2019 to October 2021 as the analysis interval, and screened out 210 pieces of effective investment and financing data about Digital Therapeutics at home and abroad through mining and cleaning investment and financing data from VB Data. We tried to discover the ever-changing development tendency of Digital Therapeutics industry through basic analysis and crossover analysis of financing amount, round, time, location of financing enterprises and investment organizations.

Data clarification: For statistical purposes, we follow the following principles in processing investment and financing data.

- Financing events involved herein include the venture capital investment events from the angel round to pre-IPO, and exclude mergers & acquisitions or secondary market financing.
- The angle round, seed round and seed VC are merged into the angle round; all rounds with A are merged into Round A; all rounds with B are merged into Round B; all rounds with C are merged into Round C; the rounds before D and the rounds before IPO are merged into Round D/D+; "Other" includes private equity financing, strategic financing, debt financing, donations, etc.

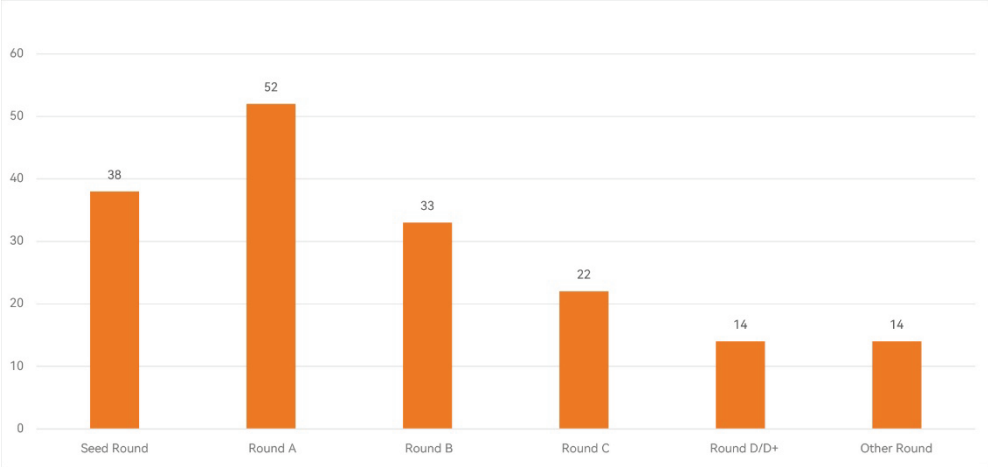
- The time of data samples herein is from January 1, 2019 to October 31, 2021. The data published after October 31 are not included in the scope of statistics.
- The amount herein is measured in U.S. dollars (the amount conversion is based on the average exchange rate in the year when the event occurred).
- The financing amount of millions/ten millions/billions is classfied into one million/ten millions/billions.
- Financing events listed in the tables and charts only cover the events in which the financing amount is disclosed, excluding those without disclosure of the financing amount.

Amount Distribution in Different Financing Rounds of International Digital Therapeutics (USD 100 Million)



Since 2019, there have been 210 financing events with disclosed financing amount in the international Digital Ttherapeutics field, involving 144 enterprises in 21 countries and regions, with a total amount of USD 8.271 billion.

Event quantity distribution in different financing rounds of international Digital Therapeutics field



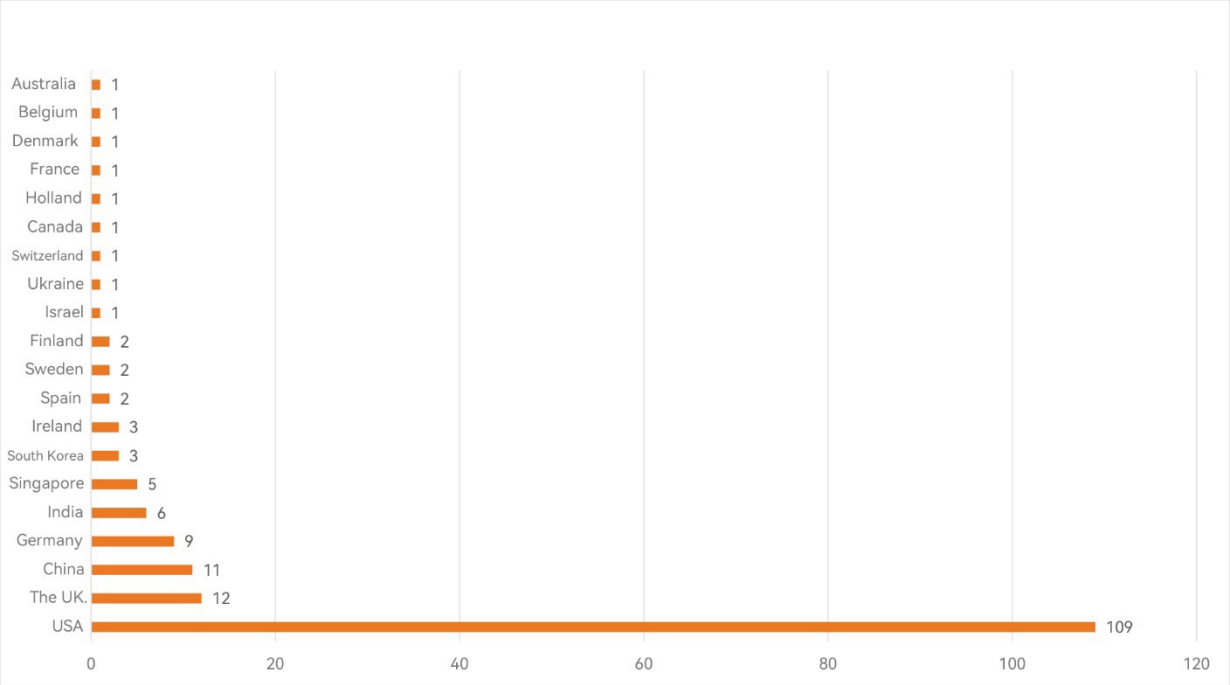
In the data statistics, there were a total of 173 financing events with disclosed financing amount and rounds, involving 123 enterprises in 20 countries and regions, with a total financing amount of USD

6.605 billion. Among them, 109 financing events happened in the United States, with the financing amount of USD 5.394 billion. On January 3, 2019, Verily (Life Sciences Department of former Google X; its Project Baseline platform could provide real world evidence support services of Digital Therapeutics) completed the private equity financing of USD 1 billion. This is also the financing event with the biggest single financing amount at home and abroad within the analysis interval. In February 2021, Otsuka Pharmaceutical and Click Therapeutics cooperated to launch a 10-week remote randomized controlled clinical trial based on Verily's Platform. In the trial, 540 participants taking single antidepressants were recruited, and they were intervened with Digital Therapeutics to assess its efficacy on adults with severe depression.

Most project financing rounds are in Round B and earlier, accounting for over 71%. This means most projects are in the rapid development stage, and the industry is very trending. Thus, capital is required to support follow-up product innovation and marketing, and the financing demand is large. In addition, although the number of Round A financing events is far ahead, the ranking of the total financing amount is low, indicating that the single financing amount is not high and the market development presents the trend of “trotting”. Investment institutions are also in the state of waiting and seeing.

A total of 14 financing events entered Round D/D+, involving 11 enterprises in China, the United States and the United Kingdom, among which 7 enterprises are Digital Therapeutics enterprises for chronic disease control, and 4 are psychotropic Digital Therapeutics enterprises. Two enterprises show the fastest financing progress: Hinge Health and Noom, both of which are Digital Therapeutics enterprises for chronic disease. In Round E financing of Hinge Health, the investors are Tiger Global and Coatue Management. It plans to launch its first IPO in 2022. In Round F financing of Noom, the investors include Silver Lake, Sequoia Capital, Samsung Venture, Temasek, RRE Ventures, Novo Holdings and Oak HC/FT, and Goldman Sachs has been employed to lead the preparation for IPO. The first IPO is predicted at the beginning of 2022.

Number of Investment and Financing Events in Different Countries and Regions



Seeing from the countries and regions of investment and financing events, North America is far ahead. There were 109 financing events in the United States, accounting for 63%, and the financing amount was USD 5.394 billion, accounting for 81%. Hence, the United States plays an important role in the global Digital Therapeutics industry. Moreover, there were 36 financing events for Digital Therapeutics in Europe, and the number is 26 in the Asian-Pacific region. There was only 1 financing event for Digital Therapeutics in Australia.

2.7 Global approval of Digital Therapeutics

2.7.1 Specific approval policy of Digital Therapeutics

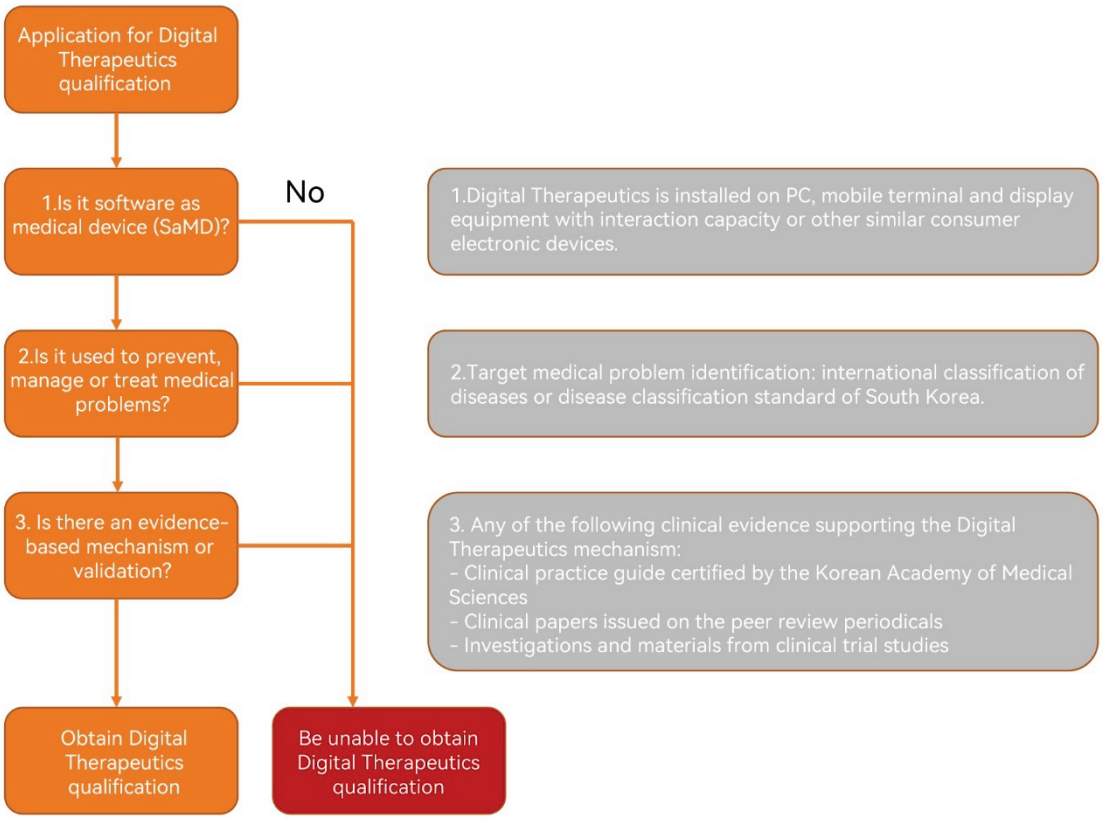
Since Digital Therapeutics is still at its very early stage, its definition and regulation are not really clear, and there is no special policy for Digital Therapeutics in the overwhelming majority of countries and regions around the world. Most countries and regions paying attention to digital health technology including the United States put Digital Therapeutics under the regulatory framework of digital medicine. There are few countries and regions enforcing exclusive policies for the implementation of Digital Therapeutics, while South Korea and Germany are the typical representatives.

Non-mandatory policy

South Korea has not approved its first Digital Therapeutics yet, but its first approved clinical trial for Digital Therapeutics started as early as July 2019 - the Ministry of Food and Drug Safety (MFDS) approved Nunap Vision clinical trial of Nunaps. In October 2020, MFDS issued the *Guideline on Review*

and Approval of Digital Therapeutics (For Industry) to guide the scope and standard of Digital Therapeutics examination and approval for the industry. This Guideline is based on the mandatory *Act of Medical Devices* as well as approval, reporting and review requirements of medical devices. However, this Guideline does not require compulsory enforcement, but aims to guide the industry.

Role of *Guideline on Review and Approval of Digital Therapeutics (For Industry)* on the accreditation of Digital Therapeutics qualification



The *Guideline* gives an explanation of the definition of Digital Therapeutics. MFDS holds that, the accreditation of Digital Therapeutics is mainly based on Chapter II of *Act of Medical Devices* and the above table.

The *Guideline* summarizes the approved Digital Therapeutics across the world, holding that a product is qualified to become Digital Therapeutics only when it has the materials of scientific (clinical) evidence about the mechanism of action, and can be classified into the Digital Therapeutics of various clinical fields according to the characteristics (applicable patients and mechanisms of action).

The *Guideline* also details the description of products which may be considered as Digital Therapeutics, and the products are classified into two categories: prevention & chronic disease management, and disease treatment.

I. Prevention & chronic disease management:

- The software which provides corrective and relaxation therapy for epileptics through the behavioral cognitive therapy to prevent recurrent epileptic seizure
- The software which controls drug dose for the patients who lose vision due to macular degeneration and posterior polar degeneration to prevent blurred vision
- The software which provides cognitive rehabilitation training for patients with mild cognitive impairment to prevent Alzheimer's disease
- The software which provides drug dose control for schizophrenics to reduce and control schizophrenia symptoms through drug therapy
- The software which manages side effects of drugs in patients with gastric carcinoma through controlling drug dose and monitoring adverse reactions like nausea and pain
- The software which reduces symptom relapse for migraine patients through cognitive behavior therapy management
- The software which helps patients with oligomyopathy to recover through exercise intervention and rehabilitation training management
- The software which helps hypertension patients to maintain normal blood pressure through blood pressure monitoring and medication management
- The software which helps patients with insulin dependent diabetes mellitus to maintain and manage the normal blood glucose level through controlling the drug dose according to patients' blood glucose level

II. Disease treatment:

- The software which enhances physical functions and relieves dyspnea symptoms through high-intensity load adjustment therapy to help patients with chronic obstructive pulmonary disease for treatment
- The software which helps patients quit smoking through the cognitive behavior therapy to reduce the symptoms of mental and behavioral disorders caused by smoking
- The software which relieves the symptoms of patients with bipolar affective disorder through the cognitive behavior therapy
- The software which controls levodopa dose through analyzing patients' conditions to reduce tremor in patients with Parkinson's disease
- The software which provides virtual reality for patients with asthma/chronic obstructive pulmonary disease to reduce the incidence of symptoms such as dyspnea and cough
- The software which treats patients with mental and behavioral disorders due to alcoholism through the cognitive behavior therapy

- The cognitive-behavioral therapy software for chronic insomniacs
- The treatment software of psychological education and cognitive behavior correction for patients with major depressive disorder
- The cognitive-behavioral therapy software for schizophrenics
- The software which provides the exposure therapy based on the virtual reality technology for patients with post-traumatic stress disorder
- The software which treats bulimia in patients with bulimia nervosa through the cognitive behavior therapy
- The software which treats functional defecation disorder in patients with irritable bowel syndrome through the cognitive behavior therapy

In addition, the *Guideline* also provides a series of explanations for the approval method. These explanations involve technical document preparation, product operation mechanisms (especially clinical evidence), indications, soft and hardware specifications and performances, warning and test specifications. The *Guideline* will lay a foundation for the release of peremptory norms for Digital Therapeutics in South Korea.

Mandatory policy

Germany created the DiGA directory for Digital Therapeutics in the directory of medical device approval. DiGA is the abbreviation of Digitale Gesundheitsanwendungen in German, with the meaning of digital health application (to facilitate understanding, Digital Therapeutics herein is DiGA). BfArM believes that Digital Therapeutics contains a wide range of possibilities, such as disease diagnosis and treatment, and self-driven healthy living habits. It is expected to become a digital assistant for patients. Since the application approval for Digital Therapeutics and traditional software is not exactly equal, after explorations for a period of time, BfArM designed a special fast approval procedure (The Fast-Track Process for DiGA) for Digital Therapeutics under the guidance of Section 139e of *Fünftes Buch Sozialgesetzbuch* (*SGB V*). On May 27, 2020, The Fast-Track Process for DiGA was officially implemented. As of December 22, 2021, the application for 114 Apps was submitted through The Fast-Track Process for DiGA, including 84 temporarily approved Apps and 30 officially approved Apps. Among the 114 Apps, 27 were approved; 7 Apps were poorly evaluated; the developers of 57 Apps voluntarily withdrew the application; 23 Apps were in process.

I. Definition of Germany Digital Therapeutics

BfArM firstly defined Digital Therapeutics, holding that Digital Therapeutics refers to Type I and Type IIa medical devices which pass CE certification of the EU and are based on EU Medical Device Regulation (MDR) and EU Medical Devices Directive (MDD) (as MRD completely replaces MDD, the new Digital Therapeutics must completely follow the requirements of the new version of MDR), and has the following attributes: The medical function of Digital Therapeutics should be implemented

mainly by digital functions of the software; it can support disease identification, monitoring, treatment or alleviation, or identification, monitoring, treatment, alleviation and compensation of physical injury or disability; it can be oriented to patients alone or to patients and medical institutions at the same time. It can be easily seen from the definition that there are differences between CE certification and Digital Therapeutics approval. Simply speaking, having CE declaration does not mean the approval of German Digital Therapeutics. But the approval of German Digital Therapeutics means it has certainly obtained CE declaration..

According to the definition of German Digital Therapeutics, medical device is its essence. BfArM has set the detailed and operable guide for the public and developers to quickly distinguish general healthcare applications and Software as Medical Device (SaMD). There are two circumstances according to whether the software application is classified as a medical device. Once the software is identified as a kind of Software as Medical Device, it shall meet the same supervision requirements as the traditional medical devices in the manufacturing process, without any exception. The first category is the identified SaMD. As per the *Act of Medical Devices*, software applications including smartphone Apps can be classified as SaMD when they meet the use for human beings and at least meet one of the four purposes. The four circumstances are as below: The software is used to diagnose, prevent, monitor, treat or alleviate diseases; it is used to diagnose, monitor, treat, alleviate or compensate physical and psychological damages or physiological defects; it is used for investigation, replacement or modification in the anatomical or physiological process; and it is used to control female fertility. In general, BfArM believes that any independent software based on data or information can be classified into a certain grade of medical devices. However, this does not cover the software only used to provide knowledge or information. For example, an electronic instruction is clearly not a medical device.

The second category is the software which may be identified as medical devices. The purpose description of such software generally includes the following words: alarm, analysis, calculation, detection, diagnosis, interpretation, conversion, measurement, control, monitoring, amplification. The software and medical devices that can be identified as a certain grade mainly include the following types: aid decision-making Apps represented by the supply of treatment measures; Apps that are used to calculate drug injection dose (excluding the way that only a simple sheet facilitating users to infer the injection dose is duplicated); the Apps that are used to monitor patients and collect data, with significant effects of monitoring results on the diagnosis or treatment. Pure data storage, archiving, lossless compression, communication, or simple information search Apps cannot be classified as medical devices. For example, a certain type of software which is specially used for data archiving is obviously not a medical device.

If a simple classification is carried out according to purposes. In most cases, decision-making support software, software system, remote medical system, HIS and PACS belong to the scope of medical devices, and operating system software and software of general purpose are not medical devices. The classification of health software Apps is obscure. To determine whether such software is classified as

medical devices, we should confirm whether it is prepared for medical use – if it is only used for exercise, fitness or nutrition, and the developer claims that there is no medical purpose, it is usually not a medical device. Some developers may try to evade regulation in the manner of "touch ball", e.g. labeling "this is not a medical device" in the App store. In view of such a situation, the *Act of Medical Devices* also explicitly stipulates that, once the software describes or implies the expected medical use in the label, instructions and other open materials, it still will be deemed as a medical device by BfArM.

For the sake of safety, Germany regulates that Digital Therapeutics can only contain Type I and Type IIa software and medical devices. In the EU, apart from the type of in vitro diagnosis and active implantation of medical devices, medical devices are classified into different risk categories based on potential damages caused by errors/faults, including Type I (low risk), Type IIa or IIb, and Type III (high risk). Type IIb medical devices may exert potential and irreversible significant impacts on human health in a certain manner. For example, Regulation 10 says that, the active devices that meet the condition that "the devices are used to provide the energy absorbed by human body (excluding the devices designed to illuminate the patient's body in the visible spectrum), used for radiopharmaceutical distribution imaging in vivo and used for direct diagnosis or monitoring of important physiological processes in human body" and that are used for diagnosis shall belong to Type IIa medical devices. However, once the physiological signs monitored by such active devices used for direct diagnosis or monitoring of important physiological processes are extremely important, they are likely to directly cause patient's life in danger (such as ECG index, breathing and central nervous system activity). Such devices will be classified into Type IIb medical devices. According to the older version of MDD, medical Apps on the smartphone and tablet PC will be classified into Type I medical devices. Certainly, if the devices are used for diagnosis or monitoring of vital signs (such as ECG index), they may be classified into Type IIa or IIb medical devices according to the degree of risks. Once they are classified into Type IIb medical devices, they will not be defined as Digital Therapeutics, and shall meet higher regulation requirements. In other words, BfArM holds that Digital Therapeutics must be highly safe and cannot produce potential dangers to human health. The software Apps that will make users caught in potential risks in the event of any anomaly cannot be defined as Digital Therapeutics. Meanwhile, the software which is only used to collect and transmit data or controls devices cannot be defined as Digital Therapeutics. The Apps that are used alone by doctors to treat patients are not Digital Therapeutics, either. Germany holds that Digital Therapeutics must have an interactive process with patients. If the devices are only used to collect data from sensors or mobile phones and transmit the data to doctors, they are not Digital Therapeutics.

In most circumstances, Digital Therapeutics will be combined with other hardware, software or services. Based on the previous experience, BfArM has provided the detailed analysis for corresponding possibilities, including the combination with other hardware, software or services, combination with other functions and disease prevention.

1. Combination with other hardware, software or services

Germany believes that there are many forms of Digital Therapeutics, such as common mobile Apps, desktop Apps or browser Apps on the computer. Digital Therapeutics can be combined with hardware or software, as long as its main functions are implemented by the digital technology applied by the software. BfArM has provided very detailed reference about whether the combination of hardware and software belongs to Digital Therapeutics.

Identification Examples of Digital Therapeutics Combined with Software and Hardware

	Desktop or browser Apps		Combination with software	Optional software
Description of DiGA identification	Web Apps which provide digital visual training for low vision patients through online virtual institutions.	Description of DiGA identification	The chest band is used to monitor apnea events caused by apnea syndrome all night long, and the App is used to remind users of the times of apnea events. Besides, the App also integrates continuous heart rate increase data collected by the smartwatch which has passed the medical device approval to provide more accurate records and assessments. If necessary, further diagnosis may be introduced.	Based on the real-time data, the App reminds patients to take analgesics and gives injection advice. It allows users to receive reminders from the smartwatch (optional) about recommended analgesic dose and directly confirm the operation.
Reason	As long as the requirements are met, both browser or desktop Apps can be identified as DiGA.	Reason	DiGA has a decisive effect on further diagnosis, and supports disease identification and monitoring.	DiGA supports the treatment of non-critical diseases, and the optional hardware will not change its major functions.
Description of non-DiGA identification	N/A	Description of non-DiGA identification	The chest band is used to monitor the patient's apnea events caused all night long, and the App will remind users of the	The platform supports multiple types of approved DiGA and also supports the smartwatch. It provides data input,

			times of apnea events.	result registration and reminding functions.
Reason	N/A	Reason	The major function of measuring apnea events is not completed by the App.	It purely provides a platform, and the main function is provided by other DiGA rather than the platform itself, so it cannot be identified as DiGA.

Digital Therapeutics can also be combined with extra services. In principle, additional services similar to those provided by consultants, training or commercial insurance can be provided by or integrated into the use of Digital Therapeutics. It is required to clarify that such extra services will not be paid by health insurance. Based on the precondition that Digital Therapeutics can be paid by health insurance, the description about the positive effects of software Apps required for approval on medical treatment cannot cover such extra services. Moreover, developers should list all application scenarios in which extra services are applied during the communication with BfArM to avoid misunderstanding. Certainly, the above circumstance is not applicable to the services provided by the doctors certified by health insurance. The services which are provided by the doctors certified by health insurance such as attending physicians, resident physicians, dentists or psychologists and related to the purpose of Digital Therapeutics are paid by health insurance in the manner of doctor services. Hence, these services can be deemed as a part of materials required for the approval of Digital Therapeutics. If the services provided by the doctors certified by health insurance can be included in the use process of Digital Therapeutics in the form of text description, or EBM code required for payment by health insurance can be directly listed (in most cases, every payment item of health insurance in Germany has an independent EBM code). It is necessary to note that these services must be provided by the doctors certified by health insurance and the reimbursement certificates must be submitted, or else health insurance payment is unavailable.

Identification Examples of Digital Therapeutics Combined with Services

	Combination with psychological counseling services		Combination with nutritionist services
Description of **DiGA** identification	The App provides a digital medical model for patients with mild depression. The App can push disease information to patients, record patients' tone of voice, register their symptoms, support the private diary function, provide relaxation exercise guide for patients and support the chatting robot function. If necessary, the	Description of DiGA identification	The App provides a digital medicine model for patients with chronic enteritis. The App can push disease and nutrition information to patients, and archive symptoms through diary or other ways. The App can guide patients to customize nutrition protocols and assess the protocols through the intelligent algorithm.

	App contacts the certified doctors or psychologists to connect the patient in the event of major depressive disorder.		Furthermore, the App can be equipped with the food scanning and assessment function to provide patients with digital nutrition guidelines. The App also provides chatting robot consulting services.
Reason	The App has the digital medicine model, completely meeting the requirements of **DiGA** for medical services. What is worth mentioning is that if the services contain the service from the doctors certified by social health insurance, it should be underlined in the description.	Reason	The App has the digital medicine model, completely meeting the requirements of **DiGA** for medical services.
Description of non-DiGA identification	The App is an online exchange platform on which psychologists assess patients' psychological status through communicating with patients via video, voice or text.	Description of non-DiGA identification	The App is applicable to patients with chronic enteritis. In the App, nutritionists (service providers of non-medical level) provide consulting services for patients through chatting or phone function.
Reason	The core function of the App is to purely achieve the digital path of dialogues, excluding further treatment services. Besides, it does not provide more services other than face-to-face, remote or video communications.	Reason	The main function of the App is provided by a “quasi-medical” institution, which has certain instability. Once the institution cancels the nutritionist service, the main service function will no longer exist.

With regard to the correlation between online medical care and Digital Therapeutics, BfArM holds that if the major function is implemented by the software digital technology, the application of online medical care is a part of Digital Therapeutics. But, a pure online medical care platform cannot be identified as digital technology. From the perspective of the scope, the scope of Digital Therapeutics is larger than that of online medical care. However, individual special cases should be confirmed after communication with BfArM.

2. Scope identification in combination of other functions

Sometimes, Digital Therapeutics will provide extra optional services or functions, e.g. connection with social media; cooperation with extra hardware and software; or the situation where the model contained has passed the approval alone as a medical device. BfArM believes that its boundary is that

these extra functions or services can neither exert any impact on the expected medial function of Digital Therapeutics when it is examined, nor endanger or change its positive influence on medical care. In addition, these functions should be independent relative to Digital Therapeutics. Even if the function goes wrong, it will not affect the basic functions of Digital Therapeutics.

Identification Examples of Digital Therapeutics Combined with Additional Functions

	Combination with multiple functions		Combination with multiple functions
Description of DiGA identification	The App is applicable to patients with migraine. The medical device has passed CE certification, and can record symptoms in the way of diary. Besides, it can integrate diary data, remind patients when migraine symptoms are more likely to occur and guide them to take preventive actions and precision therapy. In addition to these, the App also provides the paid social network function. Users can exchange with other patients via social networking services. Statement: According to Section 33a of *SGB V*, this paid social networking function will not bring about any impact on the functions of DiGA.	Description of DiGA identification	The App contains multiple modules which have passed the medical device certification individually. Module 1 provides a digital model applicable to depression. The module can record patients' psychological status, make an assessment and obtain the push of depression-related symptoms and the guidance for “mindfulness” treatment. Module 2 is designated for psychologists. It will prompt a doctor when judging the patient's condition tends to deteriorate, and the doctor can shorten the interval of psychotherapy and control the disease.
Reason	The App has the digital medicine model, completely meeting the requirements of DiGA for medical services.	Reason	The whole App containing Module 1 and Module 2 can be identified as DiGA. When a doctor issues the prescription, the services provided must be clearly labeled. During DiGA identification, Module 2 cannot be removed, because this will lead to the potential obstacle of the prescription. The App can meet safety and applicability of CE-certified medical devices only in the complete state, and must be clearly labeled.
Description of non-DiGA	The App is applicable to patients with migraine. The medical device has passed CE certification, and	Description of partial DiGA	The App contains two medical device modules which have passed the approval separately.

identification	can record symptoms in the way of diary. Besides, it can integrate diary data, remind patients when migraine symptoms are more likely to occur and guide them to take preventive actions and precision therapy. To avoid the supply of further clinical evidence of medical efficacy, the App excludes the guide module from DiGA.	identification	Module 1 contains a digital medicine module suitable for hypertension which can help patients obtain and archive their blood pressure. Meanwhile, it can push symptoms of hypertension and its complications and prevention information to patients. Module 2 designated for doctors to make assessments, and can combine patients' symptoms to provide dynamic prescription advice for doctors.
Reason	The main function of the App must be included in the expected purpose of the CE-certified medical device. If the function meets partial function of the expected medical purpose, the App must specify the function boundary approved by DiGA. The customized part of the medical device cannot be claimed as an independent product and cannot be identified as DiGA.	Reason	Module 1 is classical DiGA - it is labeled as an individual medical device and meets requirements of DiGA. Besides, the safety and applicability of Module 1 are separated from Module 2 so that the two modules can be certified separately. Module 2 mainly provides treatment support for doctors, which does not conform to the definition of DiGA.

According to relevant provisions, BfArM will not approve additional functions at present. Certainly, if the additional functions need to be paid, the expenses shall be completely borne by users themselves and health insurance payment is unavailable. Therefore, these additional functions must be labeled separately and it is required to clearly state that they are not the certified functions of Digital Therapeutics.

3. Identification of disease prevention scope

Whether the software application for disease prevention is identified as Digital Therapeutics will depend on specific circumstances. In the German medical system, disease prevention is divided into several levels. The primary prevention is targeted at the general population, which is used to prevent disease onset. In short, the primary prevention is suitable for healthy people. It can promote healthy lifestyles in specific forms (such as health courses) and be used as a means of health assessment. However, according to the definition of German Digital Therapeutics, Digital Therapeutics is used to "support disease identification, monitoring, treatment or alleviation, or identification, monitoring, treatment, alleviation and compensation of physical injury or disability". The definition clearly specifies it does not contain the function of disease avoidance or prevention and is not suitable for healthy

people. Thus, the software application only used for primary prevention is obviously not Digital Therapeutics. The software application for the secondary prevention which is mainly used to prevent disease progression and the software application for the tertiary prevention which aims to prevent complications meet “disease treatment” in the definition of Digital Therapeutics. However, the premise of passing the approval is that the disease has a specific risk factor, and the specific risk factor can be encoded as a specific disease code through the disease coding system.

Description of German Digital Therapeutics Combined with Weighing Scale

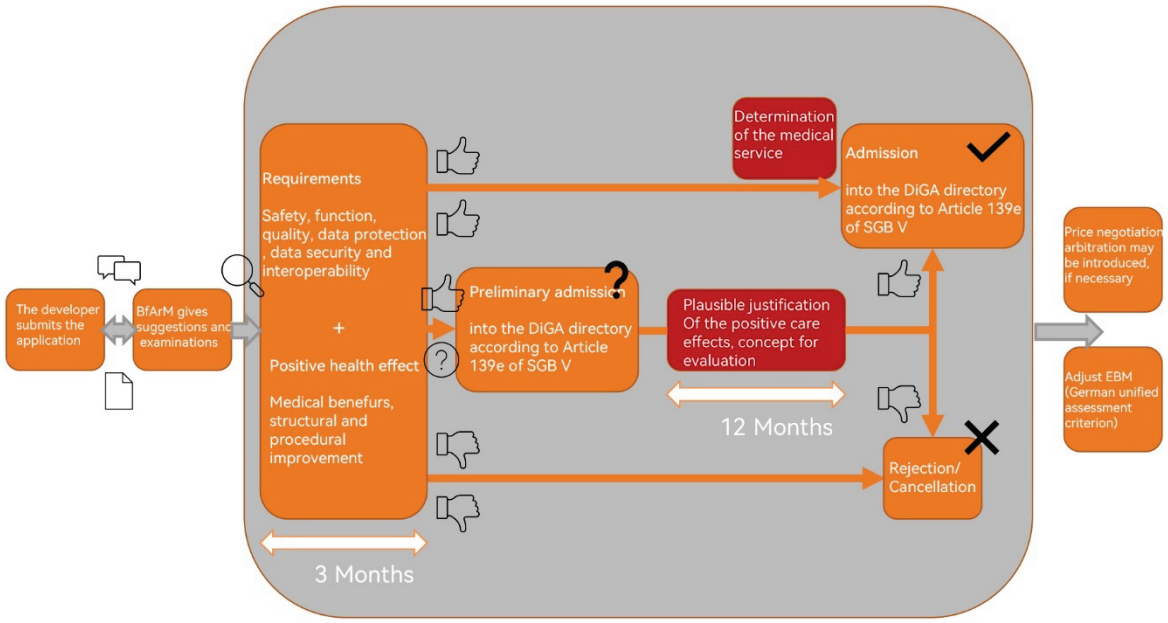
	Combination of Apps with weighing scales
Description of DiGA identification	The scale is used to measure a patient’s weight and assess the body fat rate. The software is responsible for data archiving and visualization. Besides, weight control and monitoring are a part of more complex additional applications. The App can push nutrition and fitness information, or a series of similar services provided for hypertension patients like endurance training plans.
Reason	The software is suitable for treatment of hypertension patients, and it can also be used as the secondary prevention for long-term cardiovascular disease.
Description of non-DiGA identification	The scale is used to measure a patient’s weight and assess the body fat rate. The software is responsible for data archiving and visualization.
Reason	The decisive function of measuring the weight and estimating the body fat rate is not the major function of the software application. If the software only displays data, it cannot be identified as a medical device.
Description of non-DiGA identification	The scale is used to measure users' weight and assess the body fat rate. The software is responsible for data archiving and visualization. Besides, weight control and monitoring are a part of more complex additional applications. The App can push nutrition and fitness information, or a series of similar services provided for healthy people like endurance training plans.
Reason	The App mainly aims at healthy people, which belongs to the scope of primary prevention. It does not meet the requirements of "disease identification, monitoring, treatment or recovery", so it cannot be identified as Digital Therapeutics. Due to the lack of medical purpose, it cannot be identified as a medical device, either.

4. Fast approval procedure

According to *Fünftes Buch Sozialgesetzbuch, SGB V*, corresponding guidelines shall be provided for the approval of Digital Therapeutics. BfArM specially designed the fast approval procedure and standardized the details of this procedure. Once corresponding software application is approved by BfArM, it is identified as Digital Therapeutics and included in the official directory of Digital Therapeutics. Then, the Digital Therapeutics can be used by the doctors certified by health insurance for patients, and paid by health insurance. Germany stipulates that BfArM must evaluate Digital Therapeutics applied for within three months from the time when a developer submits the application

for the App. Through investigating the product quality statements (such as data protection, interactivity and user experience) and assessing the evidence of the App effect on medical care (the possible influence of the App on improving users' health status or treating their diseases), BfArM will decide whether the Digital Therapeutics is approved.

Approval Procedure of Digital Therapeutics in Germany



The approved Digital Therapeutics will be listed in the DiGA directory, and it is required to ensure all participants in the German medical system can obtain useful information. Such information not merely includes the information that the Digital Therapeutics listed in the directory benefits medical care, and health insurance payment information, but also covers software data protection and compliance information of medical device regulations. Such information can be classified into five categories.

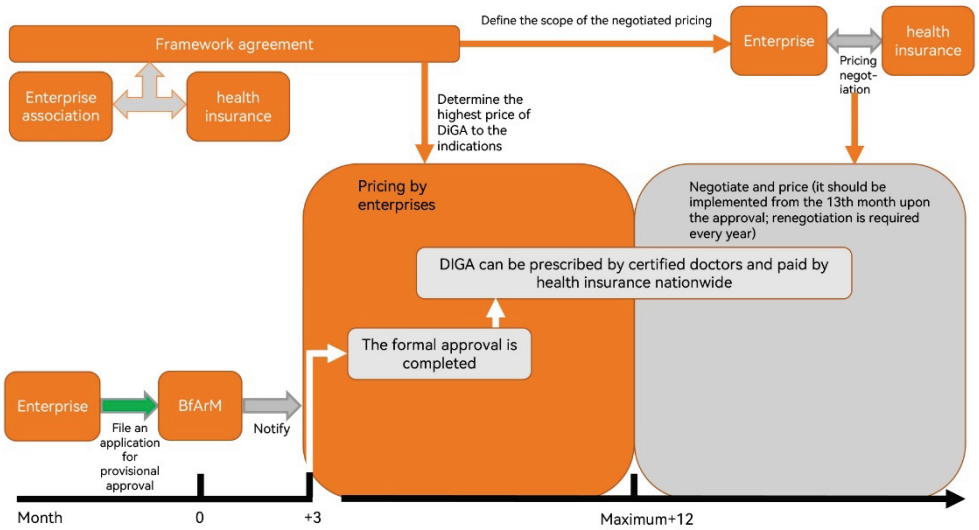
Five Categories of Information Required in the Directory of German Digital Therapeutics

Information category	Information purpose	Main content
Basic data and information of medical devices	Be used to help the regulatory authorities and users to distinguish DiGA and manufacturing information.	Developer, product name, DiGA directory number, notary organization participating in medical device certification (if the medical device certification is obtained by this way), medical purpose as stated according to the Act of Medical Devices, product description and description of developer's liability insurance, etc.
Information provided for the insured of health insurance	Facilitate the insured to search symptomatic DiGA in the directory or compare similar DiGA.	Design objective and principle of DiGA, content and function, data security, quality list and extra self-payment (if any).
Information provided for medical institutions	Facilitate medical institutions to issue prescriptions for the most applicable scenarios of DiGA, and let the certified doctors clearly know whether DiGA is associated with other services, no matter whether these services are provided by the certified doctors issuing prescriptions or by other certified doctors.	provisional approval or formal approval of DiGA, probation period for provisional approval, information that has been proven or is to be proven to benefit medical care, sensitivity and specificity of the disease examination device (if DiGA includes this device), recommended shortest and longest course of treatment, required services (if any) of certified doctors associated with DiGA and relevant health insurance payment information.
Information for medical experts	Professional medical teams, associations and other organizations can act as an opinion leader promoting DiGA, and DiGA assessment and recommendations they provide can help doctors, the insured and other target audiences to find out the suitable DiGA. Thus, relevant professional information should be provided.	Clinical studies and reports beneficial to medical care (the studies and reports are completed within one year and published on open publications), professional trial evaluation institutions of DiGA (if any) and corresponding future studies, etc.
Technical information	Be used to ensure the users can smoothly use DiGA and export data, and the data format can be used in the future.	Compatibility information of relevant platforms, devices and additional functions provided by developers as well as data interaction standards and configurations, etc.

5. Difference between formal approval and provisional approval

The BfArM also provides details on exactly how to apply – developers need to decide whether to apply for formal or provisional approval when applying for Digital Therapeutics. To a large extent, this depends on whether the applicant can provide medically beneficial, comparable clinical data on Digital Therapeutics. If medically beneficial, comparable clinical trials on Digital Therapeutics have been completed at the time of application, then formal approval can be applied for.. If the clinical trial data are recognized, BfArM will approve and list it in the directory within 3 months upon the date of application. If the first formal application fails due to some reasons (e.g. the clinical study of the App with medical benefits is not recognized), the applicant should file an application again within 12 months upon the date when the application is rejected, and new evidence must be submitted. The applicant cannot immediately apply for a provisional approval due to the rejection of the formal approval. Certainly, this will not happen, if the applicant withdraws the application before BfArM makes its final decision. Hence, nearly half of applicants withdraw their applications as disclosed by BfArM. BfArM recommends that if the applicant cannot determine whether the study beneficial to medical care can meet the requirements, prior consultation may be conducted.

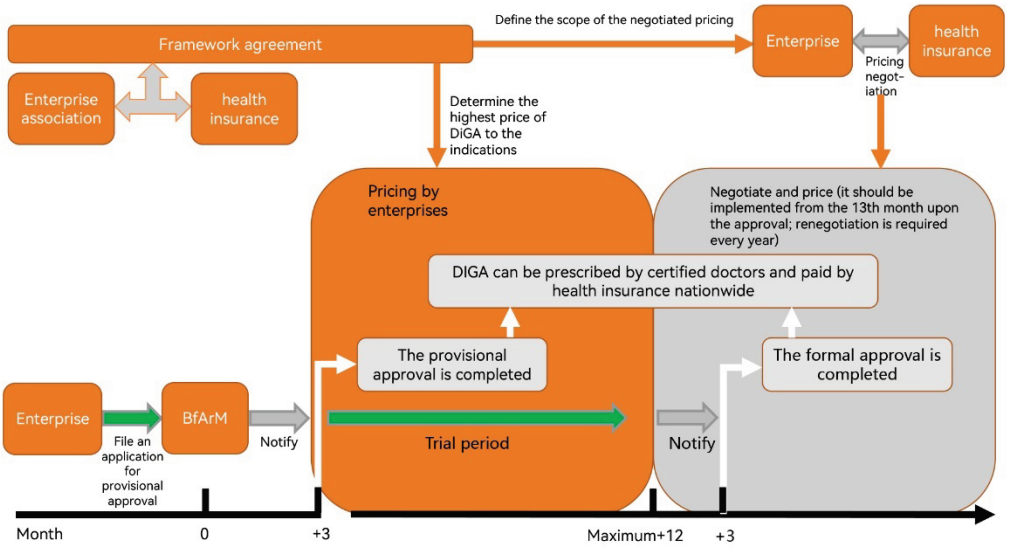
The Fast-Track Process for DiGA (Formal Approval)



Applicants who have not completed comparable clinical trials may apply for provisional approval. Interim approval requires completion of comparable clinical trials and submission of appropriate evidence of the medical benefit of the Digital Therapeutics during the trial period. The trial period will be determined by BfArM and will not exceed a maximum of 12 months, and BfArM will decide whether to convert the current provisional approval to a full approval within 3 months of receipt of these clinical data. If a comparable clinical trial report of medical benefit of DiGA is not provided within the specified period or the report fails to pass the review, BfArM will cancel the provisional approval of

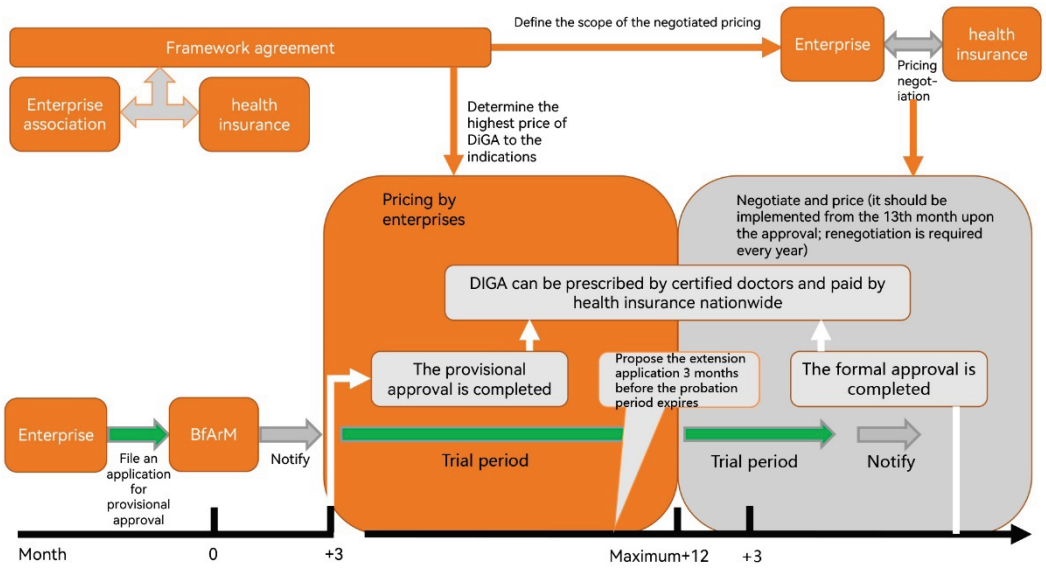
the application and remove it from the catalog. Once removed from the catalog, the developer may only submit a new application 12 months after the date of removal and must provide different clinical data than before. Applications submitted based on duplicate clinical data will be rejected.

The Fast-Track Process for DiGA (provisional Approval)



In general, provisional approval receives lower Statutory Health Insurance payments than formal approval. When applying for provisional approval, applicants will need to negotiate with the National Association of Statutory Health Insurance Funds to determine the maximum payment for the first year once full approval is completed; also, applicants will need to provide a lower priced payment cap for the trial period. In addition, developers may receive legally mandated payments from the National Association of Statutory Health Insurance Funds for the trial period of provisional approval for Digital Therapeutics, but will be responsible for the costs of clinical studies conducted during the same period. It is worth noting that BfArM emphasizes that it only approves the software application itself, and once approved, it will be paid by the National Association of Statutory Health Insurance Funds. Whether the approved Digital Therapeutics also has a version with a different business model (such as the common free advertising model) does not affect the approval.

The Fast-Track Process for DiGA (Application for Extension of Probation Period of provisional Approval)



In some cases, there is a maximum of one probationary period extension request for provisional approval. The duration of the trial period extension is determined by BfArM and can last up to 12 months. A trial extension may only be granted if clinical data for the Digital Therapeutics have been submitted as required and the BfArM determines from the data that there is a high probability of medical benefit, but the conclusions and reports have not been completed at this time. Applicants requesting an extension of the trial period must do so at least 3 months before the original trial period ends to allow sufficient time for review.

6. Application materials for The Fast-Track Process for DiGA

The Guideline of BfArM explicitly lists the materials required for Digital Therapeutics approval, including the list of software applications, safety and applicability description of software applications, data protection, information security, interactivity and further quality requirements. It is not difficult for the overwhelming majority of applicants to meet these requirements. Hence, the key to determining whether the software application can pass the approval and become a kind of Digital Therapeutics is whether the evidence to prove the positive influence of the software application on medical care is convincing.

"Evidence of medical benefits of Digital Therapeutics" is defined in *Fünftes Buch Sozialgesetzbuch, SGB V. German Law of Digital Medicine Insurance* and *German Regulations on Digital Health* applications further specify the definition, the evidence of medical benefit can be reflected in the benefits in medical care and improvements in the structure and processes of patient-related medical services. The software application should prove that the Digital Therapeutics has at least one piece of evidence of medical benefits. The medical benefits are mainly reflected in the improvement of user's health, shorter duration of illness, longer life and improvement of quality of life. The materials must

be based on patients and especially reflect the decrease in patients' incidence rate and fatal rate or improvement of quality of life. The improvements in the structure and processes of patient-related medical services are the foundation of German health insurance system payment. These improvements mainly cover the following: disease diagnosis, monitoring, treatment or alleviation, physical and psychological damages, or physiological defect diagnosis, treatment, alleviation or compensation; the medical process used to support the patient's formation of healthy lifestyles or to integrate medical institutions and the patients; and specific implementation guidelines and standards which contain treatment process coordination and are used to ensure the treatment efficacy; reduction of difficulty in visiting relevant medical services; decrease in the inconvenience of daily life caused by diseases or alleviation of the workload of patients and their families to treat diseases. In principle, Digital Therapeutics should be able to improve its position in medical care through information acquisition, direct participation or aid decision making, and reduce resource consumption resulting from treatment through the means provided by the Digital Therapeutics. During the approval of Digital Therapeutics, the evidence of the above two aspects must be provided. In addition, the applicant may submit potential impacts covering two fields and benefiting medical care - in specific conditions, it may exert positive impacts on future health insurance payment. This is not a mandatory requirement, and is totally decided by the applicant. But, once it is provided, relevant application materials should meet relevant regulations.

BfArM requires that Digital Therapeutics applicants shall explicitly define the target population, and the data of medical benefits must be obtained from at least a defined group of applicable patients. The certified doctors can only issue prescriptions for such patient population and obtain payment from the health insurance. Hence, it is necessary to define and distinguish applicable patient population through ICD-10 coding. Once the approval is obtained, the Digital Therapeutics can be directly seamlessly connected with various information systems (such as DGR and outpatient payment) encoded by the ICD coding system and the applicable patient population should be differentiated. For example, by this method, it is very clear whether a kind of Digital Therapeutics is applicable to Type 2 diabetic patients or Type 2 diabetic patients with specific complications.

To prove the software application benefits medical care, the developer must issue the control experiment results to demonstrate the effect of the software application. In the experiment, the software application should be deemed as a part of the treatment for patients. In the control group, multiple control methods (e.g. no treatment, no use of the software in the treatment or the use of other approved Digital Therapeutics in the treatment) should be adopted for comparison. Based on detailed requirements, the study may be a clinical study or an epidemiological study. Besides, the use of research methods designed for other science fields (e.g., medical, social or behavioral research) also conforms to the regulations, provided that they are appropriate to the chosen field and the study is a quantitative and comparative study. The real world research data are also allowable.

These studies must meet the requirements of Digital Therapeutics approval in multiple aspects, mainly including four aspects. Firstly, the study must be performed with Germany. In individual cases, if the

comparative evidence of applicable medical scenarios can be provided, the data acquired outside Germany can also be recognized. Secondly, the controlled study must be registered at a compliant open research institute. Compliance means the registration institution must be the main registration institution or cooperative institution of the WHO International Clinical Trial Registry Platform, or the data provider of the platform. In Germany, this institution generally refers to German Registry for Clinical Study (DRKS) subordinate to BfArM. The completed clinical data can also be submitted here. Third, the study should meet relevant internationally recognized standards for future use for demonstration and research purposes. Applicants are required to submit at least one retrospective comparative study, such as a case-control study, a retrospective cohort study, or an intra-individual comparative study. At any time, applicants may submit prospective comparative studies, i.e., studies with a fundamentally higher level of evidence. Fourthly, study data should be published and meet release regulations of relevant papers. The data also should be submitted as required by BfArM. For example, BfArM requires the publication of passive data in the clinical study. Besides, the corresponding clinical study data should be submitted to BfArM before the data have not been published and have been recognized by the clinical research registry.

Compared with the formal approval, the research data of medical benefits may not be submitted for the provisional approval, but the applicant still needs to explain that the Digital Therapeutics can reach at least one beneficial potential impact on medical care for the specific patient population. The applicant can submit systematic literature and evaluation or the system evaluation data of the software application. Based on the above content, BfArM can judge whether they can support the provisional approval. At the same time, the applicant needs to submit the evaluation protocol based on generally accepted scientific standards, and the data evaluation results should be properly considered. There should be at least one copy of documents provided by a third party independent research institution to describe how the evidence of medical benefits required for the formal approval is obtained in the design protocol. The third party independent research institution shall not have a conflict of interest against the applicant, but it can collect corresponding remuneration according to the market standards. As mentioned above, at most one application can be filed for the Digital Therapeutics passing the provisional approval, and the probation period can be extended for at least 12 months to meet the requirements of clinical studies. However, such circumstance can only occur under the condition that BfArM is very likely to draw a conclusion of medical benefits based on the existing data. During applying for the extension for the probation period, the applicant must provide justifications to explain why the evidence of medical benefits cannot be provided in the first phase of the experiment. Furthermore, good causes may be provided as required to explain why the extension of the probation period can generate the actual missing evidence. Most luckily, the Digital Therapeutics approved temporarily may obtain the 24 months of probation period in total. Even so, since many kinds of Digital Therapeutics take effect through subtly changing users' living habits, it is still believed that it may be hard to verify medical benefits within just two years. Thus, BfArM also suggested in the Guideline that, in principle, the study may start before the application for the Digital Therapeutics so as to effectively solve this problem.

Compared with the approval of Digital Therapeutics in other countries and regions, The Fast-Track Process for DiGA is comprehensive, fast and professional. Firstly, it is comprehensive. Although most countries and regions have some regulations on medical health applications, no country or region can provide a detailed approval procedure which ranges from legislation to regulations and even covers various exceptions. From this perspective, The Fast-Track Process for DiGA is second to none in terms of the comprehensiveness and integrity. Secondly, it is fast. Germany takes full account of the rapid update of software applications, if the required information is complete, the approval can be completed within 3 months after the application. This is a piece of good news for numerous small and medium enterprises, which can greatly reduce time and money costs. Thirdly, it is professional. In The Fast-Track Process for DiGA, they especially considered the medical property of Digital Therapeutics, regarded the evidence of medical benefits as the key supporting material, put forward strict conditions from research design to final submission to ensure the approved Digital Therapeutics can indeed help patients. In Germany, medical APPs are approved independently from medical devices, even though there is no corresponding special procedure in the United States. This is a very innovative move of Germany. Finally, it is convenient to pay. Once it is approved, based on the degree of improvement of the preparatory work (even supply of ICD codes of indications), the Digital Therapeutics can enter the market rapidly. The certified doctors issue prescriptions for patients and the cost is paid by the health insurance.

2.7.2 Approval status

At present, the United States and Germany are the most active countries and regions around the world in promoting Digital Therapeutics. We have made statistics of global 191 major Digital Therapeutics enterprises about FDA approval. Over the years, FDA has issued more the 50 medical device registration certificates related to Digital Therapeutics.

Time	Enterprise	Product name	Certification type
November 2021	AppLiedVR	EaseVRx	De NOVO
November 2021	MetaMe Health	Regulora	Type II
September 2021	Welldoc	Bluestar Rx	Type II
September 2021	Renovia	Leva Pelvic Health System	Type II
June 2021	Mahana Therapeutics	Parallel	Type II
June 2021	Cognoa	Cognoa ASD Diagnosis Aid	De NOVO
June 2021	Voluntis	Insulia Diabetes Management Companion	Type II
May 2021	Bigfoot Biomedical	Bigfoot Unity Diabetes Management System	Type II
January 2021	Theranica	Nerivio, FGD000075-4.7	Type II
November 2020	Mahana Therapeutics	Parallel	De NOVO
November 2020	Nightware	Nightware Kit	De NOVO
October 2020	Theranica	Nerivio	Type II

Time	Enterprise	Product name	Certification type
June 2020	Akili Interactive Labs	Endeavor	De NOVO
April 2020	WellDoc	Bluestar Rx	Type II
April 2020	Livongo	Livongo Blood Glucose Monitoring System (BG1000)	Type II
March 2020	Reciprocal Labs Corporation (Propeller Health)	Propeller Sensor For Symbicort	Type II
March 2020	Pear Therapeutics	Somryst	Type II
January 2020	NuvoAir	Air Next	Type II
November 2019	WeLLDoc	Blue Star	Type II
November 2019	Renovia	Leva Pelvic Digital Health System	Type II
August 2019	Biofourmis	Biovitals Analytics Engine	Type II
August 2019	VoLuntis	Oleena	Type II
May 2019	Theranica	Nerivio Migra	De Novo
March 2019	Biofourmis	Rhythmanalytics	Type II
February 2019	Hygieia	D-Nav System	Type II
December 2018	Pear Therapeutics	ReSET-0	Type II
September 2018	RightEye	RightEye Vision System	Type II
August 2018	Reciprocal Labs Corporation (Propeller Health)	Propeller Sensor for Neohealer	Type II
August 2018	Palo Alto Health Sciences	Freespira	Type II
May 2018	MindMaze	MindMotion Go	Type II
April 2018	Renovia	Leva Pelvic Floor Trainer	Type II
February 2018	Glooko	Glooko Mobile Insulin Dosina System	Type II
December 2017	Takeda Pharmaceutical (Baxalta US)	MyPKFiT For ADVATE Version 2.0	Type II
November 2017	Voluntis	Insulia Diabetes Management Companion	Type II
September 2017	Pear Therapeutics	ReSET	De NOVO
June 2017	Voluntis	Insulia Diabetes Management Companion	Type II
April 2017	MindMaze	MindMotion Pro	Type II
January 2017	Welldoc	Welldoc Bluestar, Welldoc Bluestar Rx	Type II
November 2016	Voluntis	Insulia Diabetes Management Companion	Type II
November 2016	Reciprocal Labs Corporation (Propeller Health)	Propeller Sensor Model 2015-E	Type II
November 2016	Welldoc	Welldoc Bluestar (Welldoc Diabetesmanager System And Diabetesmanager-Rx System	Type II

Time	Enterprise	Product name	Certification type
June 2015	Proteus Digital Health	Proteus Digital Health Feedback Device	Type II
May 2015	Reciprocal Labs Corporation (Propeller Health)	Propeller System	Type II
July 2014	WellDoc	Welldoc Diabetesmanager System And Diabetesmanager- Rx Syste	Type II
May 2014	Reciprocal Labs Corporation (Propeller Health)	Propeller Sensor-Model 2	Type II
February 2014	Proteus Digital Health	Proteus Patch, Proteus Ingestible Sensor (Accessorv)	Type II
June 2013	Proteus Digital Health	Proteus Patch Including Ingestible Sensor	Type II
May 2013	Proteus Digital Health	Proteus Patch Including InaestibLe Sensor	Type II
July 2012	Reciprocal Labs Corporation (Propeller Health)	Asthmapolis System	Type II
February 2012	WellDoc	Welldoc Diabetes Manager System And Diabetes Manager Rx System	Type II
October 2011	WellDoc	Welldoc Diabetes Manager System And Diabetes Manager Rx System	Type II
July 2010	WellDoc	Diabetesmanager System, Diabetesmanager-Rx System Model Version 1.1	Type II

FDA Approval of "Digital Therapeutics"

After FDA approved the first kind of Digital Therapeutics - De Novo in 2017, the approval of Digital Therapeutics has shown the rising trend in recent years: There were 6, 7 and 8 Digital Therapeutics approval events in 2017, 2018 and 2019, respectively; there were 9 Digital Therapeutics approval events in 2020 and 2021, respectively. It is necessary to note that due to the particularity of approval (extension and change of registration certificate), the actual number of Digital Therapeutics products is obviously lower than that of approval events.

De Novo approval of FDA refers to the approval channel in which the listed and comparable medical device cannot be found, somehow reflects the innovation. So far, a total of 7 Digital Therapeutics products have obtained the De Novo approval. Especially in 2020, 3 Digital Therapeutics products obtained the De Novo approval, while the number was 2 in 2021. Before this, only 2 Digital Therapeutics products obtained the De Novo approval. On the one hand, FDA has paid more and more attention to digital health technology; on the other hand, affected by the pandemic, FDA has attached more importance to digital health technology, further promoting the development of digital health technology. Seeing from the indications of these innovative products, pain, they correspond to multiple symptoms such as irritable bowel syndrome, post-traumatic stress disorder, autism in children, drug addiction.

According to the statistics, the 52 approvals of Digital Therapeutics involved 23 enterprises. Relative to the total of 191 enterprises, only 12% of enterprises obtained the approval from FDA – It is easy to see that the difficulty in obtaining the approval of Digital Therapeutics is quite considerable.

Product name	Enterprise	Type of approval	Platform	I ICD-10	Indication description	Supplementary payment	Additional device
CANKADO PRO-React Onco	CANKADO	provisional approval	iOS/Android/Web	C50	Malignant tumors of the nipple and areola	None	None
companion parella powered by medi - proved by Dt. Knieaesellschaft	PrehApp	provisional approval	Web	M22.2 M22.4 M76.5	Patellar disease Chondromalacia patellae Patellar tendon inflammation	None	None
deprexis	GAIA	formal approval	Web	F32.0 F32.1 F32.2	Mild depression Moderate depression attacks Severe depression attacks without psychotic symptoms	None	None
elevida	GAIA	formal approval	Web	G35	Multiple sclerosis	None	None
ESYSTA App& Portal- Digital Diabetes	Emperra	provisional approval	iOS/Android/Web	E10 Ell	Type 1 diabetes with coma Type 2 diabetes with coma	None	Optional
HelloBetter Stress and Burnout	GET. ON Institut tur Online Gesundheitstraining s GmbH	formal approval	Web	Z73	Problems related to life management difficulty	None	None
Invirto- The therapy against anxiety	Sympatient	provisional approval	iOS/Android	F40.00 F40.01 F40.1 F41.0	Agoraphobe Agoraphobe with panic disorder Social phobia Panic disorder (paroxysmal sudden anxiety)	None	None
Kalmeda	mynoise	provisional approval	iOS/Android	H93.1	Tinnitus	None	None
M-sense migraine	Newsenselab	provisional approval	iOS/Android	G43	Migraine	None	None
Mawendo	Mawendo	provisional approval	Web	M22	Patellar disease	None	None
Mika	Fosanis	provisional approval	iOS/Android	COO C01 C02	Malignant lip neoplasm Sublingual malignant tumor Others and	None	Optional

Product name	Enterprise	Type of approval	Platform	I ICD-10	Indication description	Supplementary payment	Additional device
					unspecified malignant tumor of the tongue		
Mindable: Panic disorder and agoraphobia	Mindable Health	provisional approval	iOS/Android	F40.0 F41.0	Agoraphobe Panic disorder (paroxysmal sudden anxiety)	None	None
Non-Smoking Heroes App	NichtraucherHeLden	provisional approval	iOS/Android	F17.2	Mental and behavioral disorders caused by tobacco use	None	None
Novego: Coping with depression	IVPNetworks	provisional approval	Web	F32.0 F32.1 F33.0	Mild depression attacks Mild depression attacks Mild recurrent depression	None	None
Oviva Direct for Obesity	Oviva	provisional approval	iOS/Android	E66	Obesity caused by excessive heat	None	None
Rehappy	Rehappy	provisional approval	iOS/Android	G45 160 161	Transient cerebral ischemic attacks and relevant syndromes Subarachnoid hemorrhage Intracerebral hemorrhage	None	None
Selfapys Online Course for Depression	Selfapy	provisional approval	Web	F32.0 F32.1 F32.8	Mild recurrent depression Moderate depression attacks Moderate depression attacks	None	None
Selfapy's Online Generalized Anxiety Disorder Course	Selfapy	provisional approval	Web	F41.1	Generalized anxiety disorder	None	None
Selfapys Online Course in Panic Disorder	Selfapy	provisional approval	Web	F40.01 F41.0	Agoraphobe with panic disorder Panic disorder (paroxysmal sudden anxiety)	None	None
somnio	mementor	formal approval	iOS/Android/Web	F51.0	Non-organic insomnia	None	Optional
velibra	GAIA AG	formal approval	Web	F40.01 F40.1 F41.0	Agoraphobe with panic disorder Social phobia Panic disorder (paroxysmal sudden anxiety)	None	None

Product name	Enterprise	Type of approval	Platform	I ICD-10	Indication description	Supplementary payment	Additional device
				F41.1	Generalized anxiety disorder		
Vivira	Vivira Health Lab GmbH	provisional approval	iOS/Android	M16.0 M16.1 M16.2	Primary myeloid arthropathy, bilateral Other primary myeloid arthropathy Medullary arthropathy caused by dysplasia, bilateral	None	None
vorvida	GAIA AG	formal approval	Web	F10.1 F10.2	Mental and behavioral disorders caused by excessive alcohol use Dependence syndrome caused by alcohol use	None	None
zanadio	aidhere GmbH	provisional approval	iOS/Android	E66	Obesity caused by excessive heat	None	Optional

Digital Therapeutics (DiGA) Approval in Germany (as of December 2021)

By contrast, since Germany has the special fast approval channel for Digital Therapeutics, its approval is more targeted. As of December 2021, a total of 24 Digital Therapeutics products passed BfArM approval. Seeing from the indications, most Digital Therapeutics products aim at mental disorders. This is also the field that Digital Therapeutics is good at. Furthermore, only 6 Digital Therapeutics products have obtained the formal approval. The remaining 18 Digital Therapeutics products are still in the state of provisional approval, and they need to further prove their medical efficacy before finally obtaining the formal approval. It is still difficult.

Apart from the United States and Germany, other countries and regions also have started to approve Digital Therapeutics in succession. For instance, Japan completed the approval of the first Digital Therapeutics for smoking cessation in August 2020. In general, because various countries and regions just have a preliminary understanding of Digital Therapeutics and have not improved corresponding frameworks, the corresponding approval processes are unsystematic and fragmented, still facing big obstacles. However, as the digital health technology develops continuously, the introduction of Digital Therapeutics has gradually become a trend, and it is imperative to improve and optimize corresponding approval procedures. As Germany took the initiative to improve the approval framework and process, more countries and regions will explore approval modes with their own characteristic in the future.

2.8 Global Digital Therapeutics organizations

The Digital Therapeutics Alliance (DTA) is a global promoter of Digital Therapeutics and has a large influence.. Founded in October 2017, it is a non-profit trade organization. Its founding members include Akili Interactive, Propeller Health, Voluntis and WellDoc, and then quickly incorporated industry leaders and stakeholders. As of November 2021, DTA has 70 member enterprises.

DTA is devoted to evidence-based development of Digital Therapeutics. As the leading international organization for Digital Therapeutics leadership and market education, the Digital Therapeutics Alliance provides patients, clinicians, payers and policymakers with the tools necessary to evaluate and utilize Digital Therapeutics.. DTA promotes Digital Therapeutics around the world in many ways as follows: establishing the definition of digital treatment and core principles that Digital Therapeutics must follow; making clinicians and decision makers able to adopt Digital Therapeutics and integrate it into the healthcare system so as to improve clinical and economic results of patients and the population; assisting policy makers in identifying Digital Therapeutics within the national and regional regulatory framework; promoting Digital Therapeutics, its short-term and long-term value to end users; cooperating with Digital Therapeutics enterprises and the whole ecological systems to push the development of Digital Therapeutics industry.

In 2018, Digital Therapeutics Alliance issued *Digital Therapeutics Industry Report 2018*, which firstly gave clear definition of Digital Therapeutics, and formulated the core principles and practices relating to R&D, manufacturing, clinical validation, and supervision. Since its members are all major enterprises in the Digital Therapeutics industry at that time, these definitions, principles, and guidelines basically became the default industry standards. This also became the catalyst for the development of Digital Therapeutics industry and played a key role in promoting the great development of Digital Therapeutics in the future. DTA also has driven the expansion of the Digital Therapeutics assessment framework in Europe. However, a series of baseline requirements for the digital health technology have been achieved in Europe, but there are also divergences in various countries of Europe.

DTA has also promoted the implementation of an emergency access program for Digital Therapeutics during the pandemic, with legislative and regulatory proposals designed to provide new treatment options for patients with serious unmet needs during the outbreak; and to further expand patient access to clinically evaluated digital therapies. In the meantime, DTA also presented a petition to the international governmental agency to provide clinically validated digital treatment products for citizens during the pandemic. It also proposed members to ensure and support high-quality Digital Therapeutics to improve healthcare services during the pandemic.

Based on this, DTA is also continuously pushing to improve Digital Therapeutics accessibility, such as driving public policy improvements in the United States to accelerate access to Digital Therapeutics for vulnerable people and helping individuals living in remote or medically underserved settings with public health issues. In 2020, DTA's report, *Digital Therapeutics: Reducing Rural Health Inequalities*, calls on the insurance industry to use evidence-based digital therapies to help address disparities in health care access for medically underserved populations. The reasons for these disparities are varied and include patient age, language, culture, income, disease state, or geographic location. Moreover,

DTA has established a payer advisory committee in the U.S. to engage relevant payers of Digital Therapeutics in the work of the DTA, thereby enabling payers to evaluate and demonstrate the value of Digital Therapeutics.

3. What Hainan Does in the field of Digital Therapeutics Industry

On January 25, 2022, Hainan Provincial Health Commission released the “14th Five-Year Plan for the Development of Digital Health in Hainan Province”, which included "exploring Digital Therapeutics pilot" as one of the main tasks for the development of digital health in Hainan province in its “14th Five-Year Plan”. This is also the first time in China that Digital Therapeutics has been included in the provincial planning and has received attention and promotion at the provincial level.

Article 22 of the “14th Five-Year Plan” for the Development of Digital Health in Hainan province mentions that it “will increase the promotion of Digital Therapeutics, actively introduce Digital Therapeutics products that have been approved for marketing at home and abroad, and promote their use in eligible institutions and people in Hainan to further meet the needs of residents for disease treatment and health management. Relying on Hainan Free Trade Port’s policy advantages and industrial foundation, it will promote Hainan's region-wide Digital Therapeutics application demo, explore the construction of Digital Therapeutics related policy support system step by step. Besides, it will also take multiple measures to strengthen investment, thus forming a number of Digital Therapeutics innovation highlands and industrial clusters, building Hainan into a global Digital Therapeutics innovation island, promoting ‘Digital Therapeutics + Telehealth’ aggregation and reconstruction, and creating a new engine for the high-quality development of Hainan's health industry.”

General Secretary Xi Jinping emphasized in his speech at the conference celebrating the 30th anniversary of the establishment of Hainan province and the Hainan Special Economic Zone that Hainan should "actively develop a new generation of information technology industry and digital economy", and the Notice of the Ministry of Commerce and Other 20 Departments on Several Measures to Promote Trade Liberalization and Facilitation in Hainan Free Trade Port proposed to “support the active development of digital trade in Hainan Free Trade Port”, and the “modern service industry” is one of the four leading industries in Hainan.

Digital Therapeutics represents the latest technology direction, which is the intersection of modern service industry, high-tech industry, digital economy, digital trade and other key development directions of Hainan and the innovative path for the construction of a healthy Hainan. It’s also an important step of Hainan to implement the new development concept of building a modern economic system to take the lead in the country.

In terms of specific implementation policies, in general, Hainan will actively introduce Digital Therapeutics products that have been approved for marketing at home and abroad, and promote their

use in eligible institutions and populations throughout the province to further meet the needs of Hainan residents for disease treatment and health management. At the same time, relying on the policy advantages of Hainan Free Trade Port and industrial foundation, Hainan will promote the application of Hainan-wide Digital Therapeutics Demo Zone, and explore the construction of Digital Therapeutics support policy system step by step. In addition, it will also take measures to strengthen investment, the formation of a number of Digital Therapeutics innovation highlands and industrial clusters, to promote “Digital Therapeutics + Telehealth” aggregation and reconstruction and to create a new engine of Hainan towards healthy and quality development. Ultimately, it is hoped that the policy advantages of zero tariff, low tax rate, simple tax system, relaxed market access and construction of electronic prescription center in Hainan Free Trade Port will attract innovative resources and create several innovation highlands and industrial clusters.

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