Digital Health & Digital Therapeutics in Policy Pathways of the EU and India

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Table of Acronyms and Abbreviations

ABDM	Ayushman Bharat Digital Mission
AGENAS	Agenzia Nazionale per i Servizi Sanitari Regionali (National Agency for Regional Health Services)
AI	Artificial Intelligence
ANS	Agence du Numérique en Santé (Agency of Digital Health)
B2C	Business to Consumer
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BIS	Beneficiary Identification System
CE	Conformité Européenne (European Confirmity)
C-DAC	Centre for Development of Advanced Computing
CDSCO	Central Drugs Standard Control Organization
CLIMS	Centralised Laboratory Information Management Systems
CNEDiMTS	Commission Nationale d'Evaluation des Dispositifs Médicaux et des Technologies de Santé (National Commission for the Evaluation of Medical Devices and Health Technologies)
DCA	Drugs and Cosmetics Act,1940
DCT	Decentralised Clinical Trial
DHTs	Digital Health Technology
DiGA	Digitale Gesundheitsnwendungen (Digital Health Applications)
DiGAV	Digitale-Gesundheitsanwendungen-Verordnung (Digital Health Applications Ordinance)
DMN	Dispositifs Médicaux Numériques (Digital Medical Devices)
DRKS	Deutsches Register Klinischer Studien (German Clinical Trial Register)
DTA	Digital Therapeutic Alliance
DTx	Digital Therapeutics
DVG	Digitale-Versorgung-Gesetz (Digital Healthcare Act)
EFPIA	European Federation of Pharmaceutical Industries and Associates
EHDS	European Health Data Space
eHN	Electronic Health Network
EMDN	European Medical Devices Nomenclature
EMR	Electronic Medical Record
EU	European Union
GDPR	General Data Protection Regulation
GIDH	Global Initiative on Digital Health
GKV	Gesetzliche Krankenversicherung (Statutory Health Insurance)
GKV-SV	GKV-Spitzenverband (National Association of Statutory Health Insurance Funds)
HAS	Haute Autorité de Santé (French National Authority for Health)
HCPs	Healthcare Professionals/Providers
HDFC	Housing Development Finance Corporation
HIU	Health Information Users
HMI	Hospital Management Information
HTA	Health Technology Assessment
ID	Identity
ISO	International Organisation for Standardization
IVD	In-Vitro Diagnostic Medical Devices
IVDR	In-Vito Diagnostic Regulation
IQVIA	International Quality and Value Institute Advisors
LATM	List of Telemedical Monitoring Activities
LEA	Essential Level of Care
LMIS	Laboratory Management Information System
LPPR	List of Reimbursable Services and Products
Ltd.	Limited
MD	Medical Devices

MDCG	Medical Device Coordination Group
MDR 2017	Medical Devices Rules, 2017
MDR	Medical Device Regulation
MDSW	Medical Device Software
MoHFW	Ministry of Health and Family Welfare
NB	Notified Body
NDHA	National Digital Health Authority
NDHB	National Digital Health Blueprint
NHA	National Health Authority
NIC	National Informatics Centre
NVHCP	National Viral Hepatitis Control Program
PDMDs	Patient-Managed Digital Medical Devices
PECAN	Prise en Charge Anticipée
PHR	Personal Health Record
PRA	Panel Reactive Igg Antibodies
Pvt.	Private
PZN	Pharmazentralnummer
SHI	Statutory Health Insurance
TB	Tuberculosis
TRS	Transaction Management System
USA	United States of America
USD	United States Dollar
WHO	World Health Organisation

Executive Summary

The way we optimise process and time has changed internationally due to the whirlwind adoption of digital automation, artificial intelligence, and big data. The healthcare sector has not remained untouched. Digital Health is the new solution for many policy healthcare issues in the European Union and India. The European Union and India differ substantially regarding public-private makeup, regulatory frameworks, and policy aims. However, they make suitable partners for technology exchange and trade in the healthcare sector. While the European Union stands to gain from the Indian private healthcare setup and easy availability of trained healthcare workers, India may benefit from the European Union's experience in universal healthcare. The EU and India are suited trade partners for technology, medicines, medical devices, and, finally, collaborating to get the first mover advantage in digital therapeutics promotion.

Although digital health is a widely used term, no specific definition is universally accepted. Presently, it is considered a subset of medical devices in healthcare regulations. There needs to be clarity on reimbursements for digital health. As per the author, this policy vacuum is perfect grounds for EU-India collaborations. This paper studies similarities and differences in definitions and categorisations governing digital health and digital therapeutics in the EU and India. The aim is to create adequate information and understanding early to promote collaboration in policy-making and ease trade in digital health and therapeutics.

Digital therapeutics is a subset of digital health which not only monitors or reports health data but may be instrumental in treating or alleviating diseases and create a demonstrable positive impact on patient health. Their approval and adoption require policy assistance because their registration requires clinical evidence, and their adoption requires data on real-world outcomes. If the timeline for registration is unpredictable or very long, the product can become commercially not viable before rollout.
However, the definition and classification of a medical device are already aligned to a great extent in the EU and India. This creates common ground with similar approvals and classifications for the EU and India. An attempt at creating trade ties which promote reciprocity in regulatory approval acceptance is one of the main possibilities. This can also assist with speeding up the digital therapeutics' registration process, which is imperative for their commercial success, being time-sensitive technological developments capable of quick redundancy or update.

Based on such commonalities found in definitions and classifications related to digital therapeutics, this paper suggests various steps that the EU and India can take to collaborate on digital health policies and promote trade.

1. Introduction

In 1995, Dr. Joseph Kvedar from Boston, United States of America ("**USA**") conducted a program to understand the use of technology to expand healthcare access beyond traditional hospital setup or a doctor's office, suggesting the 'one-to-many models of care'. The idea was to expand the physicians' scope by overcoming time, place, and personnel limitations restricting healthcare delivery while taking better care of patients with fewer resources by providing access, convenience, and efficiency.[1] This thought process catapulted during COVID-19 with social distancing and increasing requirements for remote advisory from healthcare professionals.

With the world plugging digital automation, artificial intelligence, and big data in every sector imaginable, healthcare is not an exclusion. Various types of products and technologies occupy the digital health sector. According to the 2021 IQVIA Report on Digital Health Trends, digital health investments worldwide had reached a substantial USD 24 billion by 2020.

In the ambit of this world market, the European Union ("**EU**")-India relations on healthcare have long stood ever since the EU-India Strategic Partnership of 2004.[2] Although the public-private makeup, regulatory frameworks, and policy aims of India's and the EU's health systems are substantially different, several elements make this sector favourable for fostering bilateral trade links and collaboration between the two. With their ageing populations, rising costs, and overburdened public healthcare systems, EU member states could stand to gain from closer ties with a nation like India, which has a burgeoning private healthcare industry, the emergence of world-class corporate hospitals, a large pool of medical talent, and a young population in a variety of demographics.

India's international health diplomacy and leadership are essential in this context. Often called the 'world's pharmacy', India recently intended to promote international digital health adoption through standardised norms through its presidency of the G20 in 2023. The World Health Organization ("**WHO**") and the G20 India presidency announced a new Global Initiative on Digital Health ("**GIDH"**) where the WHO intends to release standards and norms on digital health, assist member countries in building digital health capacities and strengthen international cooperation.[3]

The outcome document of the G20 Health Ministers Meeting under India's Presidency in 2023, which was unanimously agreed to by all G20 delegations, mentions digital health 18 times. The health declaration acknowledges how countries working in silos on digitising healthcare systems are leading to reduced country-level impact and calls for international cooperation. It also acknowledges the role and importance of digital health in achieving universal health coverage and health-related sustainable development goals.[4] Interestingly, the international declaration repeatedly acknowledges the importance of the security of health-related data and users' privacy but misses the risks created and opportunities when we do not delineate digital therapeutics- its meaning, features, risks, and growing requirement to achieve universal health coverage. This is the theme of this paper.
In this paper, we study how digital health can be categorised and defined to understand the factors necessary for policymakers when making decisions concerning its regulation and trade promotion between India and the EU. For this purpose, we have chosen Germany, France, and Italy as sample countries in the EU for a comparative study with Indian regulations and policy ecosystem.

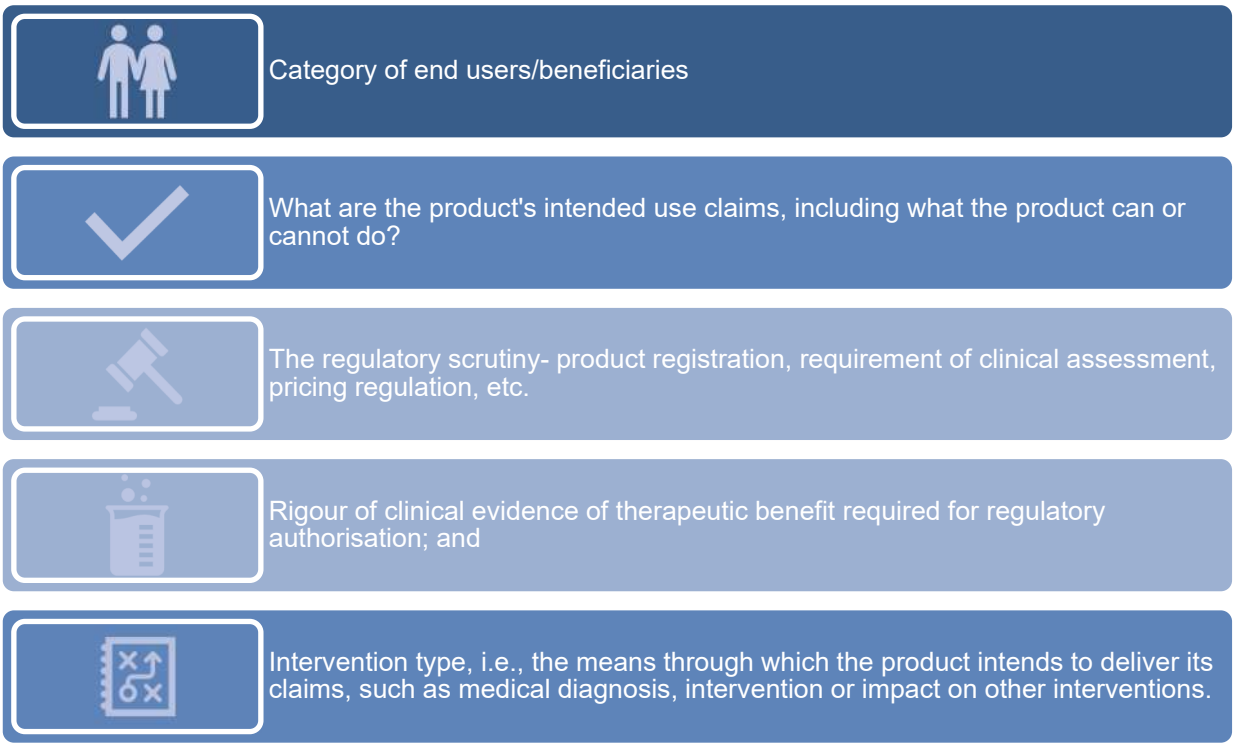
2. What is Digital Health

The term' digital health' broadens the definition of 'eHealth' to encompass digital consumers using a wider variety of smart devices and connected technology. It also includes various applications of digital technology for health, like the Internet of Things, AI, big data, and robotics.[5] Examples of digital health systems include health information technologies, telehealth systems, systems that use consumer health information, and clinical care administration tools, among others.

Of the above categories, the patient-facing Business to Consumer ("**B2C**") category has received the most attention recently. These include mobile applications targeted solely at health and wellness, e-commerce platforms for medicines, telemedicine service providers and mental health support, to name a few. There are smart applications on devices such as smart-watches, other wearables, and sensors. However, 'digital health technology' can also engulf various clinical grade categories such as digital biomarkers, medical grade decision support tools, and companion applications.

Despite the multitude of regulated and unregulated medical products in the terminology, no standard terminology or definition is used in regulations and policies, even within the EU. Nevertheless, technologies used in digital health can be categorised in various ways.

For instance, the Digital Therapeutic Alliance ("**DTA**") has created a categorisation based on the following five differentiation criteria based on the definition of digital health technologies. [5]

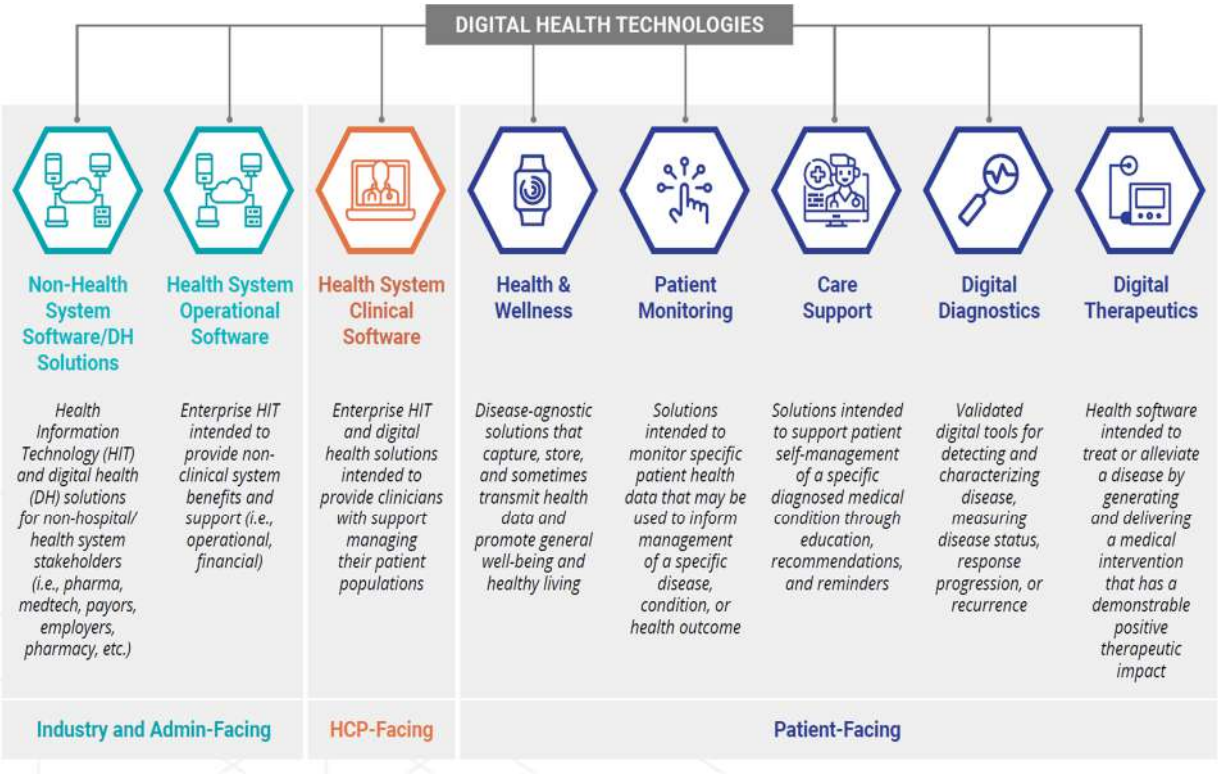


Although these products may also include physician, payer, or health system-facing features, the five patient-facing categories are solutions primarily designed for patients to use and have patient-facing features (such as mobile apps, computer software, and wearables). A basic orienting principle for how Digital Health Technologies ("**DHTs**") are evaluated, managed, and compensated is described in the order of increasing impact on clinical treatment from left to right in this subset of solutions. Regulatory scrutiny, stakeholder willingness to pay, and the bar for evidence necessary for acceptance all rise along with the rising influence on clinical management.

The three sub-categories on the left primarily cater to non-patient stakeholders, such as healthcare providers ("**HCPs**"), administrators of hospitals and health systems, and other parties involved in the healthcare sector, such as employers and payors. Most of these solutions are more related to corporate software because they are frequently centrally adopted and indirectly impact patient care, even though they may have patient-facing components (such as Electronic Medical Record ("**EMR**") user interfaces). Then, there is also the possibility of categorising such technologies based on the level of patient care necessary and the type of intervention (clinical grade or otherwise).[6]

Like the European Union, there is no definition for digital health in India. In 2017, a committee under the chairmanship of Shri J. Satyanarayana was constituted under the National Health Policy. As per the recommendations of this committee, the Ayushman Bharat Digital Mission ("**ABDM**") was constituted under the National Health Authority. The ABDM, although a policy, is more of an action plan for the government to digitise and centralise the country's entire healthcare system. This plan includes various features such as creating a digital ID for every healthcare system user of India and empanelling all the hospitals, clinics, diagnostic centres, laboratories and pharmacies, service providers and healthcare professionals on the system.[7] For instance, the present Digital Health Incentive Scheme[8] gives per transaction monetary incentives for empanelling and using the hospitals and clinics for using the digital health system. Hence, in terms of adoption, presently, the focus of the Government of India is on Health

System Clinical Software and Health System Operational Software facing healthcare professionals and ancillary service providers as per the classification of DTA.



There is growing dialogue in the European Union and our study countries of Germany, France, and Italy on the need to create awareness about digital health, bringing it mainstream and distinguishing the various levels and categories of digital health for better regulation, reimbursement and understanding among users. In India, the government, through its initiatives, acknowledges the vital role digital health shall play in making universal health coverage systems robust.

Non- Clinical Grade Options		Clinical Grade Options
• Activity and Fitness Trackers • Smart Consumer Technologies (non-medical grade) • Patient-generated Data Repositories • Wearable and Sensors (non-medical grade)	**Monitoring**	• Digital Biomarkers • Implantable • In-person or Virtual Clinical Monitoring • Remote Monitoring Tools • Wearables and Sensors (medical grade)
• Connected Virtual Assistants or Consumer Voice Assistants • Online Consumer Health Information Sources • Predictive Analytical Tools (non-medical grade)	**Diagnosis**	• Clinical Outcome Assessments • Digital Biomarkers • Digital Diagnostics • In-person, Telehealth, or Virtual Clinician Diagnosis
• Clinical Decision Support Tools (non-medical grade) • Data Repositories • Wearables and Sensors (non-medical grade)	**Treatment Decision**	• Clinical Decision Support Tools (medical grade) • Companion Applications (medical grade) • In-person, Telehealth, or Virtual Clinician Diagnosis
• Engagement Tools (social media, online communities, etc.) • Lifestyle Options (nutrition, physical exercise program, etc.) • Patient-generated Data Repositories • Wellness and Fitness Applications	**Treatment and Ongoing Care**	• Clinician-delivered in-person or Virtual Care • Digital Therapeutics (DTx)** • Non-DTx Medical Devices • Pharmaceuticals

3. Digital Health Technology as a subset of medical devices

The most common classification of digital health is in the existing regulatory framework worldwide as a subset of medical devices.

In the EU, Medical Devices ("**MDs**") are regulated by Regulation (EU) 2017/745 ("**MDR**"), and in vitro diagnostic Medical Devices ("**IVDs**"), a sub-category of MDs with their own specific legislation, are regulated by Regulation (EU) 2017/746 ("**IVDR**"). This framework is harmonised in the EU and aims to ensure the consistent functioning of the internal market. Both regulations were issued in 2017 and only recently came into complete application.

Medical devices are classified into four classes based on their inherent risk (MDR, Annex VIII): I, IIa, IIb, III. Class I includes lower-risk devices, which – except for sterile and/or measuring devices – do not require the intervention of a Notified Body ("**NB**") for CE marking; Class IIa and IIb comprise medium-risk devices; many electromedical devices fall into these classes; Class III comprises higher-risk devices, such as cardiovascular catheters. Class IIa, IIb, and III devices require the involvement of a Notified Body for CE marking. The classification of an MD is carried out following a set of rules, one of which, Rule 11, classifies Medical Device Software ("**MDSW**"). According to the MDR Rule 11, MDSW intended to provide information to make a diagnosis or therapeutic purpose decisions or monitor physiological process is classified as class IIa or above. In contrast, other MDSW is classified as class I.[9] Digital therapeutics ("**DTx**") currently on the market in Europe generally fall in class I or IIa.

Before placing an MD on the market, the manufacturer must demonstrate compliance with MDR requirements through a conformity assessment. The specific assessment route is based on device classification ((MDR, Annexes IX to XI). For Class IIa, IIb and III MDs, conformity assessment is carried out by a **NB**, an independent conformity assessment body designated by the National Competent Authority according to the MDR. For Class I MDs, the intervention of a NB is not required – except for sterile and/or measuring devices – and the manufacturer performs the conformity assessment. After the conformity assessment is favourably concluded, the manufacturer or the NB, depending on MD class, can CE mark the product, certifying the device's conformity to the MDR (or IVDR).

According to the MDR and the Medical Device Coordination Group ("**MDCG**") Guidance, only software products that, alone or in combination, have a specific medical purpose qualify as MDSW. Focusing on MDSW, which represents the most innovative and dynamic class, a first subclassification can be applied based on the intended use of the device, distinguishing products to be used by HCPs only from products intended to be used by laypersons/patients alone or assisted by an HCP.

A second level of classification may be based on whether the MDSW is **independent**, i.e., with its own intended medical purpose and intended to be used on generic hardware, or **combined** with a hardware MD, i.e., both of achieving its own independent purpose and driving the hardware; or embedded in a hardware MD, with which it forms an integral product intended to be used in the given configuration (besides having a medical purpose on its own). Indeed, software qualified as an accessory to an MD is not MDSW.[10]

Of all the possible configurations, independent and combined MDSW intended to be used directly by the patient may be called patient-managed Digital Medical Devices ("**pDMDs**"), formally defined as "stand-alone software medical devices to be used by laypersons alone or assisted by a health care professional for a medical purpose." pDMD, which covers the full spectrum of medical purposes devised in the MDR and IVDR, can be divided into pDMDs marketed until now, mainly used for therapy, diagnosis, monitoring, or secondary prevention. For pDMDs with a therapeutic purpose, Digital Therapeutics ("**DTx**") has been commonly used for years, even without an accepted formal definition.

The increasing impact of digital health services and products, coupled with the importance of sustaining and controlling the sharing of electronic health data emerged with the COVID-19 pandemic, fostered the EU legislator to provide a regulatory umbrella to protect EU citizens over their health data. To address issues related to the management, sharing and control of electronic health data, the European commission established as a priority and fundamental building block towards the construction of a

strong European Health Union, the creation of domain-specific common European data spaces in the area of health, the European Health Data Space ("**EHDS**").[11]

The EHDS, which represents the first common EU data space, is "a health specific ecosystem comprised of rules, common standards and practices, infrastructures and a governance framework that aims at

- empowering individuals through increased digital access to and control of their electronic personal health data, at national level and EU-wide, and support to their free movement, as well as fostering a genuine single market for electronic health record systems, relevant medical devices and high-risk AI systems (primary use of data)
- providing a consistent, trustworthy, and efficient set-up for the use of health data for research, innovation, policy-making and regulatory activities (secondary use of data)".[12]

When fully operational, the EHDS will provide to EU citizens easy access to and control of their health data and the possibility to easily share their data with healthcare professionals across borders. It also provides a common EU format for patients' summaries, ePrescriptions, laboratory results, image reports and other data to foster interoperability.

From the infrastructural point of view, the EHDS builds on the legislative framework on patients' rights in cross-border healthcare,[13] which established the eHealth Network ("**eHN**"), a voluntary network that connects national authorities responsible for eHealth, which aims to support the development of sustainable eHealth systems, services and interoperable applications, facilitate cooperation and the exchange of information among Member States, enhance continuity of care and ensure access to safe and high-quality healthcare. The eHN has provided a general guideline on the electronic exchange of health data, supported by Commission Recommendation on a European Electronic Health Record exchange format (C(2019)800), and guidelines on specific topics, such as ePrescription and eDispensation, Patient Summary and Laboratory results and reports.[14]

From the point of view of data security and privacy the EHDS builds on the General Data Protection Regulation ("**GDPR**"),[15] and other initiatives such as the proposed Data Governance Act[16] and Data Act,[17] and Directive (EU) 2016/1148,[18] providing a strong legal framework for the use of health data.

In India, medical devices and their software-related counterparts of digital health are governed by the Drugs and Cosmetics Act, 1940 ("**DCA**"), read with the Medical Devices Rules, 2017 ("**MDR Rules**"). Classification of MDs is dealt with under Rule 4 of MDR 2017, which states that medical devices, including digital medical devices, shall be classified based on their intended use. Further, we must take into consideration the term ***'intended by its manufacturer'*** in the definition clause of Medical Device, and the term *'intended use'* which is defined in Rule 3(v), MDR 2017, as follows,

> *"Intended Use means the use for which the medical device is **intended according to the data supplied by the manufacturer** on the labelling or in the document containing instructions for use or electronic instructions for the use of such device or in promotional material relating to such device, which is as per approval obtained from the Central Licensing Authority."*

This implies that even though there may be mobile applications and smart devices (wearables such as smart-watches, etc.) that can monitor critical human biomarkers and are widely used by the general population while making crucial health-related decisions, however, since they are not primarily marketed and designed as 'medical devices', they will not be recognised as a medical device. They are merely general wellness and care applications that do not fall within the ambit of MDR and DCA. However, wearable technological devices are proposed to be regulated under the Digital India Bill, 2023.

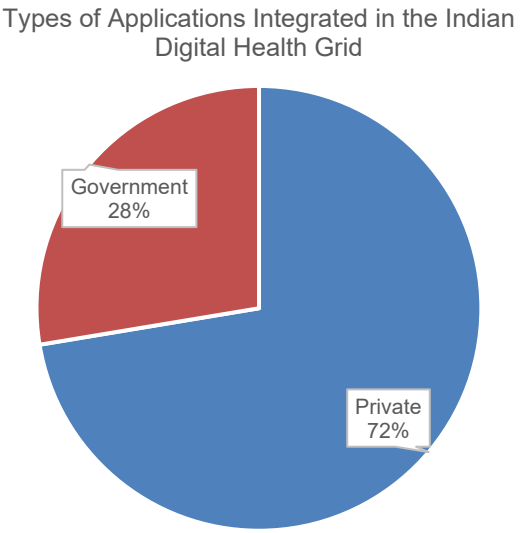
The terms 'Patient Digital Medical Devices' and 'digital health' are not expressly defined in the Indian legal framework. However, Digital Health Services are recognised by India's National Health Authority ("**NHA**").

The Ministry of Health and Family Welfare ("**MoHFW**") published the National Health Policy 2017, laying out goals for creating a 'Digital Health Ecosystem' and establishing a National Digital Health Authority ("**NDHA**"). In 2019, the then-National Health Agency was reconstituted as the NHA. This was followed by the National Digital Health Blueprint 2019 ("**NDHB**"), which laid out plans for establishing and implementing a proper framework for digital health in India.

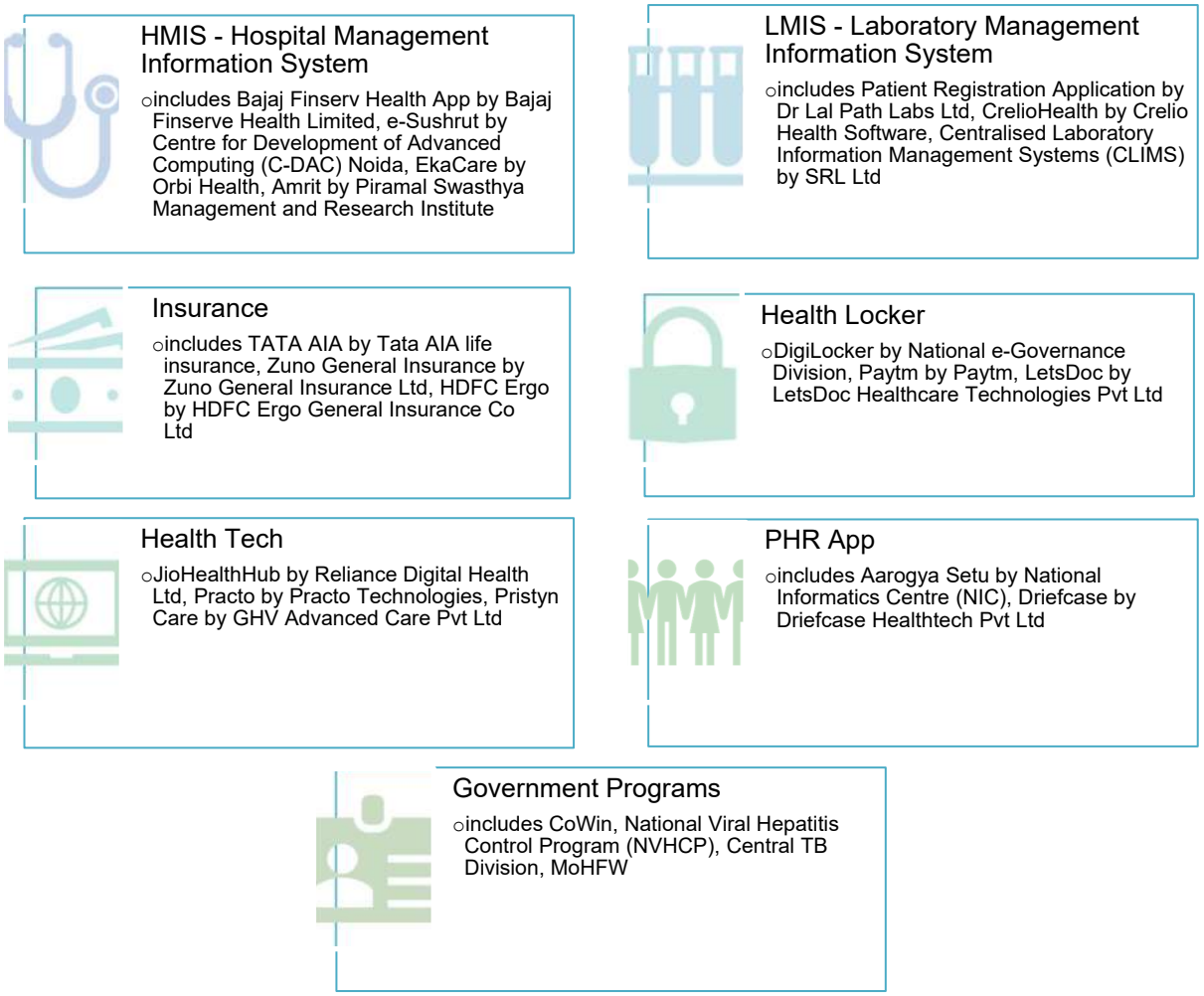
This was soon followed by the National Digital Health Mission ("**NDHM**") being launched by the MoHFW, which aimed at creating an integrated digital health ecosystem. The NDHM is now known as the ABDM and is a flagship initiative by the government to create an integrated digital health ecosystem that connects all stakeholders, such as patients, healthcare providers and insurance companies.

Further, the MoHFW revised the Health Data Management Policy draft 2022, which deals with the consent framework, sharing of personal data, data security and breach, obligations, and compliances of Health Information Users ("**HIUs**").

The ABDM provides a digital platform wherein any private software system can apply for integration and validation at the ABDM Sandbox Environment. Integrating the public and private sectors is done to collaborate and strengthen the country's digital health ecosystem. This platform is open for healthcare service providers, hospitals, vendors, health information providers, users, health lockers, etc. Currently, participation in the ABDM interface is voluntary. There are a total of 112 Digital Health Services currently which are successfully integrated within ADBM, out of which 76 are Private Sector Health Applications (e.g. PRA by Dr Lal Path Labs Ltd, Practo by Practo Technologies Ltd, Pristyn Care by GHV Advanced Care Pvt Ltd, JioHealthHub by Reliance Digital Health Ltd, etc) and 29 are Government Managed Health Applications (e.g. Aarogra Setu by National Informatics Centre, DigiLocker by National e-Governance Division, Transaction Management System ("**TRS**") and Beneficiary Identification System (BIS) by National Health Authority, etc.).



These integrated Digital Health Service Applications on the ABDM Platform are divided into 7 categories. Further, the Central Drugs Standard Control Organisation ("**CDSCO**") has classified medical devices into 24 distinct categories; one is software as a medical device, which is further distributed among 60 types of products based on their intended purpose.[19] All medical devices are categorised based on detailed parameters. The risk categorisation in India is the same as that of the EU ((i) low risk - Class A; (iia) low moderate risk - Class B; (iib) moderate high risk - Class C; (iii) high risk - Class D.)[20]



4. Definitions and Distinguishing Features of Digital Therapeutics (DTx)

Before proceeding to the regulatory definitions and classifications, it is crucial to understand where digital therapeutics feature in digital health. Now, there is no accepted definition of digital therapeutics worldwide. The international body DTA[21] has recently adopted the International Organization for Standardization ("**ISO**") definition, which is the most commonly referred direct definition:[22]

> ***Health software*** *intended to* ***treat or alleviate*** *a* ***disease, disorder, condition, or injury*** *by generating and delivering a* ***medical intervention*** *that has* ***a demonstrable positive therapeutic impact*** *on a patient's health.*

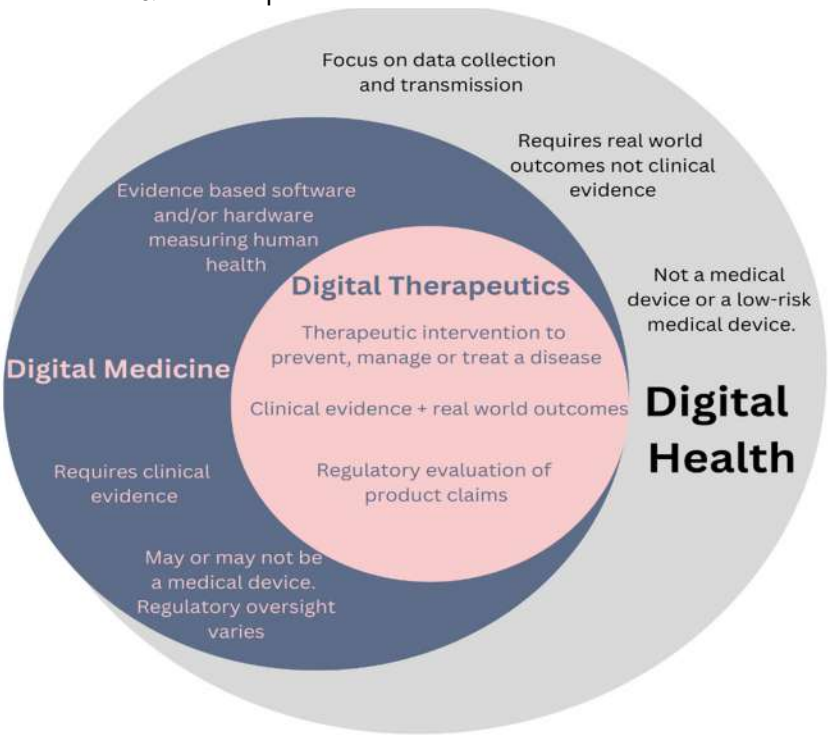
Recently, the ISO definition of DTx has not been adopted by the EU and Member States legislator. Indeed, many terms are still used in different countries for DTx.

The European Federation of Pharmaceutical Industries and Associations ("**EFPIA**") defines digital therapeutics to include the above and interventions that prevent or manage a disease or disorder. In addition to showing a demonstrable positive therapeutic impact, emphasis is placed on use to optimise patient care and health outcomes. Research by IQVIA notes that the beneficial effects of DTx result from a software program more so than the input or involvement of physicians and motivational health coaches. However, there may be communication with such parties.[23]

DTx can be used as a single treatment option or in association with pharmacological treatment. They can function as stand-alone software or in association with a hardware device that supports the therapeutical effect of the software. The digital technology must not be a digital application intended to collect data from a device and facilitate data sharing with HCP. Still, the medical purpose must be achieved through the primary digital function. DTx is intended to be used by patients or patients with the supervision of healthcare professionals but not by physicians to treat patients.

Otherwise, healthcare technologies that provide information to be shared with a physician or to trigger a healthier lifestyle, such as blood glucose meter software or devices that lead to a therapeutic decision, can be called pDMD with diagnostic function. An example of a diagnostic pDMD can be represented by a smart-watch app intended to send alarm notifications to the user upon recognising heartbeat irregularities for detecting cardiac arrhythmia. Moreover, examples of diagnostic pDMDs that interoperate with a hardware MD may be represented by the software supporting a closed-loop insulin delivery system. Finally, pDMDs that perform a direct therapeutic function, as in the case of apps, videogames, or virtual reality treatments, are usually referred to as DTx.

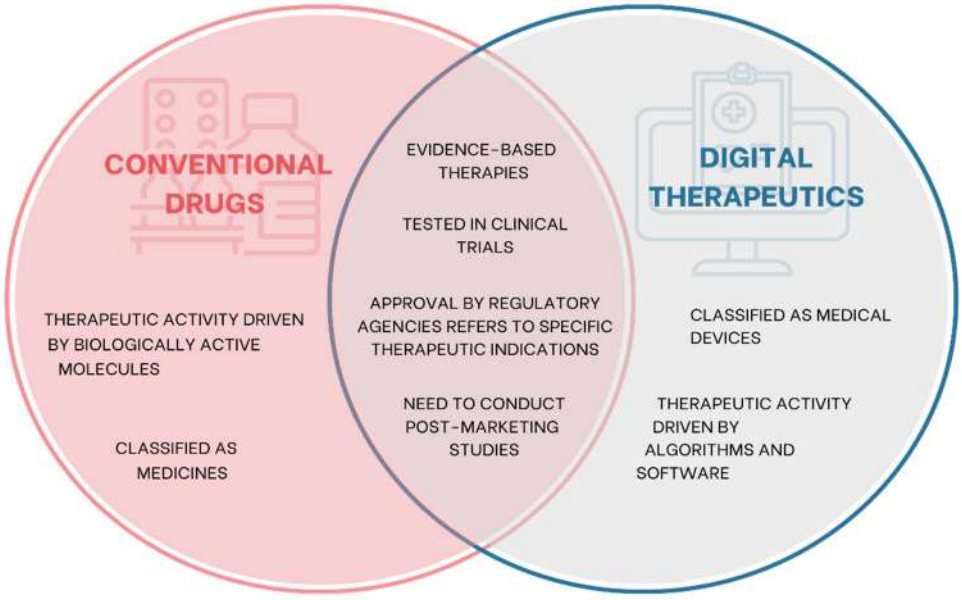
Most research papers distinguish between digital health, digital medicine and DTx to better define DTx. Digital health sub-categories are a Venn diagram where digital health encompasses healthcare and technology. Here, Digital health includes technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes; capture, store or transmit health data; and/or support life science & clinical operations.[24]



This makes digital medicine a subset of digital health. This 'nesting doll' categorisation is based on the increasing seriousness of intended claims to end users, regulatory oversight, clinical evidence requirement and risk. Here, digital medicine includes software or hardware products, typically supported by clinical evidence, to measure or intervene in the service of human health. For instance, they may be used to regulate or monitor the delivery of medicines or stimulation, such as insulin pumps, continuous glucose monitors, or track use.[25] Examples of digital medicines include digital diagnostics, digital biomarkers, and remote patient monitoring devices. Digital Therapeutics becomes a further nesting doll within the sphere of digital medicine.[26]

Here, it becomes essential to distinguish between digital therapeutics and digital medicines and digital therapeutics and conventional drugs, on the other hand.

As discussed in the definition above, DTx treat, alleviate, prevent, or manage a disease using a clinical, evidence-based therapeutic intervention. However, it is also required to prove its outcome through data on real-world outcomes. Additionally, while many digital medicines may not require regulatory approval or are non-prescription drugs, all digital therapeutics are considered to require regulatory approval before market sale or prescription, as the case may be. DTx share the characteristics of being clinically



evidence-based and tested in clinical trials. It has regulatory approval and requirements to conduct post-marketing studies with conventional drugs. However, they differ from conventional drugs because they use algorithms, software, machine learning and artificial intelligence to drive therapeutic activities instead of biologically active molecules in conventional drugs. In terms of regulatory classification as well, DTx is presently classified internationally under medical devices instead of medicines or drugs.[27]

5. Medical Devices vis-à-vis DTx in India and the EU

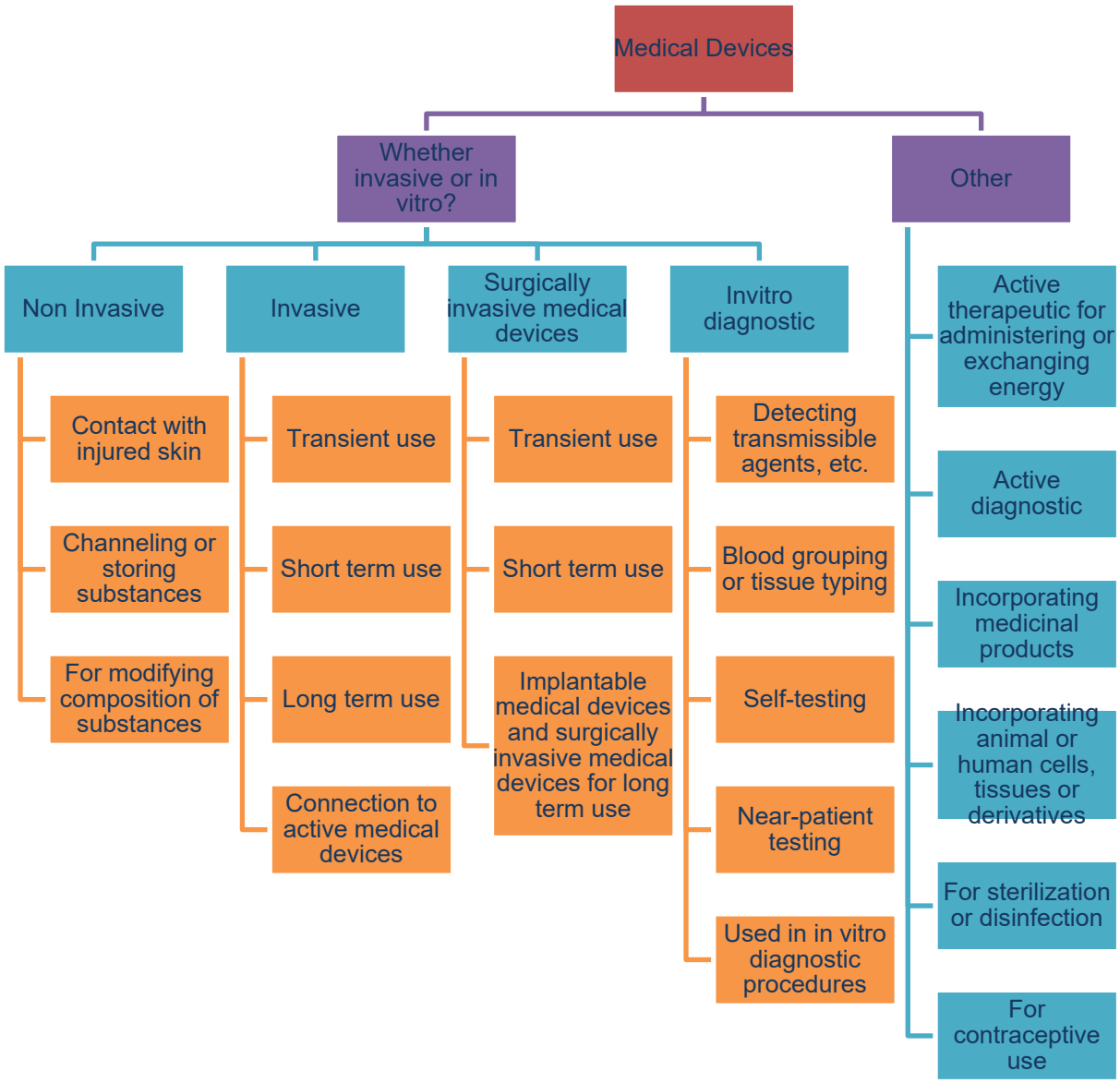
The definition of medical devices in India[28] and the EU are aligned. Both definitions categorise digital health as a medical device, either software or a combination of hardware and software. Key commonalities between the definitions of India and the EU create an excellent foundation for further integration and cooperation to promote trade and innovation. Some of the critical factors are detailed below.

Features	Common features	Differences-India	Differences-EU
Intended function	• diagnosis, prevention, monitoring, treatment or alleviation of any disease; • diagnosis, monitoring, treatment or alleviation for any injury or disability; • investigation, replacement modification or support of the anatomy or of a physiological process; • does not achieve the primary intended action in or on the human body or animals by any pharmacological or immunological or metabolic means, but which may assist in its intended function by such means • supporting or sustaining life; • disinfection of medical devices, and control of conception.	• Use of 'disorder' in addition to 'disease' • Addition of 'assistance' for injury or disability	• Additions of 'prediction', 'prognosis' • Addition of 'compensation for any injury or disability • Includes 'support' of conception • Includes products for 'cleaning' and 'sterilisation' of devices

Intended Use/ Purpose	• the use for which the medical device is intended according to the data supplied by the manufacturer; • on the label, in the instructions for use or in promotional material	Approval is required from the Central Licensing Authority	Specified by the manufacturer in the clinical evaluation
Active Device	• device, the operation of which depends on a source of energy other than that generated by the human body for that purpose or by gravity		Devices intended to transmit energy, substances or other elements between an active device and the patient without significant change shall not be considered active devices.
Sterile and/or measuring device	• Do not require prior authorisation	They need to be reported on the online portal SUDGAM	

The critical difference in the regulatory treatment of digital health and digital therapeutics category medical devices in India and the EU is the classification and the resultant clinical evidence requirements. A separate definition for 'active therapeutic medical device is provided in India. The definition contains 'digital therapeutics' terminology- 'treatment or alleviation of any illness, injury or handicap'. However, any medical device in this category must 'support, modify, replace or restore biological functions or structures'.[29] The parameters for classification in India are provided below.

Although there may be additional requirements in the EU based on whether a pDMD is healthcare professional-facing or patient-facing, no such requirements are provided in India. Further, there is an additional guidance note on the qualification and classification of software in medical devices in the EU. This is problematic because there is no emphasis on other parameters internationally accepted to be relevant in the risk classification of digital therapeutics, such as ultimate users and whether there is any decision involved or only monitoring and passing of information to a healthcare professional. While in the EU, most digital therapeutics fall in the categories I and IIa, all invitro digital therapeutics shall fall in Class C and Class D (equivalent to Class IIB and III in the EU). Additionally, subcategorisation in the active therapeutic medical device category is based on the risk involved in energy exchange. This shall not assist with the risk categorisation of digital therapeutics, which should be based on different parameters such as whether the software makes closed-loop decisions, the product claims, whether a prescription is necessary, and who is the user (patient or healthcare professional).



6. Regulatory Framework in the European Union

This section describes the regulatory framework for pDMDs with medical purpose and their accessibility in three EU Member States, Germany, France, and Italy, the first two being the ones where the products are already prescribed and reimbursed by the national healthcare system. These countries have devised different ways of identifying the concept of pDMD and developed ad hoc pathways to enable its distribution and reimbursement. The differences between the evaluation criteria and some examples of technologies are highlighted.

6.1. Germany

Thanks to the established normative framework, operational since April 2020, Germany emerges as the leading country in Europe both in terms of the number of currently provided pDMDs authorised by the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, "**BfArM**").[30] The Digital Health Technologies regulatory framework was defined within the Digital Healthcare Act (Digitale-Versorgung-Gesetz or "**DVG**") of 2019, implemented by the Digital Health Applications Ordinance[31] (Digitale-Gesundheitsanwendungen-Verordnung, "**DIGAV**") of 2020, which provides procedures and requirements for the evaluation and reimbursement of those technologies.

pDMD in Germany is called Digital Health Applications (Digitale Gesundheitsnwendungen, "**DiGA**"). DiGA are devices designed to "support recognition, monitoring, treatment or alleviation of disease or injuries" through a medical intervention with a demonstrable positive therapeutic impact on a patient's health. Indeed, the safety and efficacy of those products must be assessed by clinical trials. Moreover, they are called "digital assistants in the hands of patients" because they are intended to be only used by patients. These characteristics make the DiGA category superimposable with pDMDs, as defined here. Additionally, DiGA products have the following characteristics:

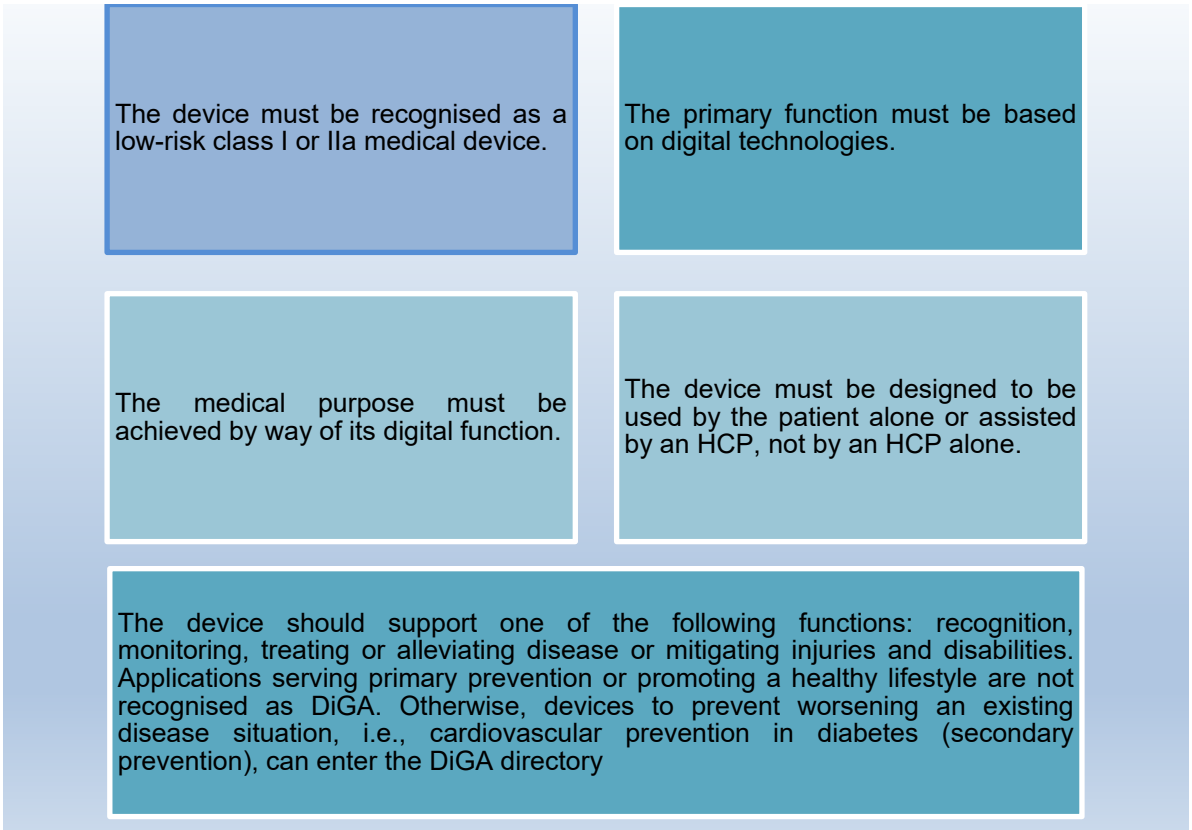
They are prescribed by a primary care physician or psychotherapist. Insured people who can provide their statutory health insurance funds proof of a corresponding indication can receive a desired DiGA without a prescription.

The competent authority for DiGA assessment and price negotiation is BfArM, the national body competent for MDs in general and medicinal products. BfArM is also responsible for uploading and regularly updating the online list of DiGA (DiGA directory).[32]

During the product assessment of DiGAs, the BfArM follows restrictive evaluation criteria. Interaction between the patient and the application is a fundamental requirement. Devices that passively collect and transmit health data from other devices (such as wearable devices or sensors) are not considered DiGA. Technologies designed to simplify communication between physicians and patients (e.g., Videocall or chat) are not classified as DiGA. Moreover, a DiGA can be a native app or a browser application, or it can also comprise a sensor, wearable, or other hardware if the primary function is pronominally carried out by the software. The hardware is only necessary to achieve the primary function made by the software, for example, by collecting data. In addition to the primary function, DiGA can also offer additional services such as consultation or coaching.

Nevertheless, the evidence for medical purposes has to be evaluated without considering this element, and they are not involved when regarding reusability. The support of HCPs is considered an additional functionality. For these reasons, DiGA are not defined as telemedicinal solutions and are profoundly different from common wellness apps.

To make such treatments available to patients as quickly as possible, the BfArM has developed a procedure that allows devices to be evaluated in a Fast-Track process: the BfArM has to evaluate the DiGA within three months after the application. The core of this assessment is the examination of the manufacturer's statements on the product quality (i.e., data protection and user-friendliness) and the examination of the evidence for a positive health effect of the DiGA. For manufacturers, the listing of DiGA in the Directory represents the decisive step towards eligibility for reimbursement with SHI. A few pre-requisites must be fulfilled before entering this pathway:



Digital health technology can enter the Fast-Track process if these requirements are met.[33] After receiving the application, BfArM has three months to evaluate the product. During this period, the regulatory body must ascertain that security, cybersecurity, functionality, and interoperability requirements are met. In addition to that, it must ensure efficacy through clinical trial evaluation. The manufacturer must demonstrate that digital therapy provides a real benefit to the patient's health that is equivalent to standard treatment, if not superior.

Suppose the manufacturer can provide all the above requirements. In that case, he can apply for final listing so that, after these three months, the product is admitted permanently into the DiGA directory, it is reimbursed and prescribable. Otherwise, applying for a provisional listing in the directory for one year will be possible if the manufacturer cannot provide sufficient evidence for a positive healthcare effect, but all other requirements are fulfilled. The device will be marked and reimbursed as a DiGA during this period, and the required study can be conducted. Suppose the device has demonstrated its performance in a clinical trial. In that case, it is reclassified from provisional to final listing at the end of this year.

After the inclusion into the permanent list, the amount of remuneration for the device must be negotiated between the manufacturer and the National Association of Statutory Health Insurance Founds ("**GKV-SV**"). Up to this point, the economic aspect is not evaluated. In the previous stage, the BfArM verifies only safety, functionality, and positive healthcare effects. Price negotiations with the insurance representative body begin after a company has been listed permanently. The producer can choose how much to charge during the temporary listing period. At the end of the year, the manufacturer must return the difference between the initial price and the negotiated one for all prescriptions sold. Analysing the price negotiation, a price reduction of approximately 40% is shown. Moreover, if the physicians have to provide additional services as part of the treatment, they are reimbursed.

Once the digital technology is accounted into the DiGA directory, it can be prescribed by primary care physicians and psychotherapists. During the prescription phase, the physician has to insert a PZN code (bar code for identifying drugs in Germany) that refers specifically to the demanded DiGA. The patient then sends the prescription containing the code to the insurance company, requiring an activation code to download and log in to the software. When the insurance company supply the code needed, it also includes additional information about the manufacturer and the link through the software can be downloaded. Once the device is obtained, it can be used for the designated period, generally equal to

3 months. At the end of this period, the patient and physician decide whether to provide a new prescription.

When the manufacturer applies for the DiGA directory, it is asked to conduct a comparative clinical trial to prove a positive healthcare effect. Even if the manufacturer applies for provisional authorisation, the trial must be started and shown that it will provide evidence of a beneficial effect on health before the submission. In this case, you are given one year to conclude the trial. If needed, the probationary period can be extended from 1 to 12 months, sending a request to the BfArM within three months of the scheduled end of the study. Once the application is evaluated and included in the directory, a clinical trial reference has to be posted on the BfArM website within 12 months of approval.

The evidence must be provided by a retrospective comparative study. "Retrospective" means investigating events that have already occurred. "Comparative" implies that comparisons are made against a control group. The following retrospective comparative studies are also accepted: case-control studies, retrospective cohort studies or intra-individual comparisons. Since the study must necessarily be quantitative comparative, the control arm for the study may include:

The chosen methodology has to be adequate for the selected object of investigation, and the method of analysis has to be chosen depending on the research question and the endpoints investigated.

Observational analytical studies, such as case-control or cohort studies, are also accepted. They may be retrospective or prospective, depending on the research question. Furthermore, experimental intervention studies, such as non-randomised and randomised controlled trials, are also appropriate. Pragmatic Clinical Trials, sequential Multiple Assignment Randomised Trials, and Multiphase Optimisation strategy may also be helpful, depending on the care context of the DiGA and the evidence sought. It is also possible to present a meta-analysis according to specific criteria included in the DiGAV.

The clinical trials must be conducted in Germany to ensure meaningful results. Moreover, no later than 12 months after the study competition, it must be published in a study registry or a partner registry of the World Health Organisation International Clinical Trials Registry Platform. The recognised primary clinical trials registry in Germany is the DRKS. Studies already completed can also be found there.

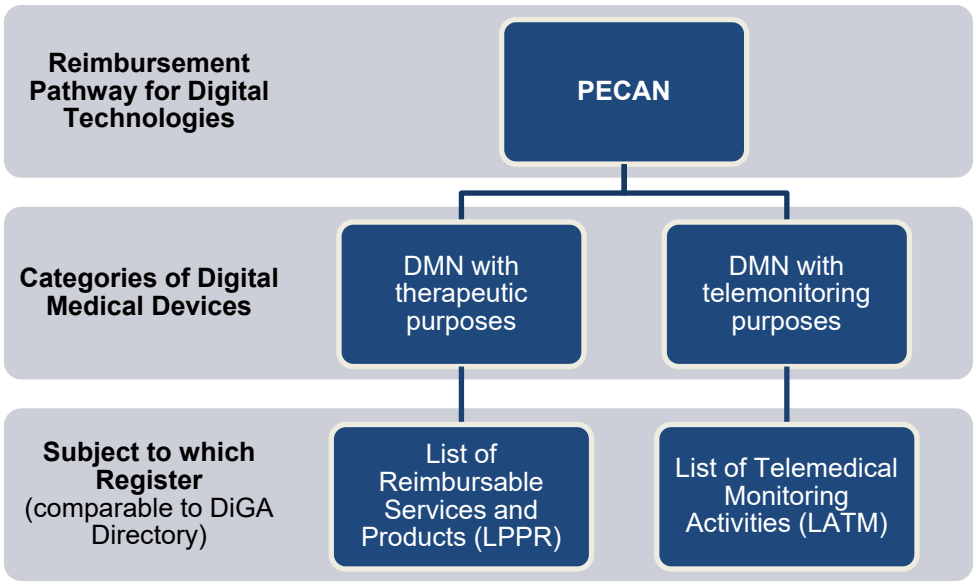
Study results must be submitted to BfArM before admission to the primary registry but not published. Negative results must also be published. It is not possible to be a candidate for both the provisional list and the final list at the same time. If BfArM rejects your application, you can reapply after one year.

At the end of the first half of 2023, we count 20 DiGAs placed on the final list and 27 on the provisional list, while 6 devices that applied to BfArM have been rejected.[34]

6.2. France

In France, Digital Medical Devices (*Dispositifs Médicaux Numériques*, "**DMN**") are subdivided into two categories: DMN with therapeutic purpose (equivalent to digital therapeutics) and DMN with telemonitoring purpose.[35]

France adopted the regulatory framework for DMN management, *Prise en Charge Anticipée* ("**PECAN**"), established in 2014 but fully operational only since 2022. The PECAN process is inspired by the Germany DIGA early management. It allows the DMN derogatory reimbursement for a one-year period while waiting to be included in the List of Reimbursable Services and Products ("**LPPR**"). This listing system allows the Health Insurance Fund to cover a list of procedures or services performed by healthcare professionals in outpatient facilities or in the hospital**.** Here, devices can be routinely reimbursed by Social Health Insurance. Specifically, Decree No. 2023-232 of 30 March 2023[36] introduces the possibility of early assessment for two categories of Digital Medical Devices relating to innovative DMN: those for therapeutic purposes intended for inclusion on the LPPR and the Remote Medical Surveillance DMN for inclusion on the List of Telemedical Monitoring Activities ("**LATM**"). In France, telemedical monitoring devices follow a different classification and have specific regulatory structures different from DMN for medical purposes.



The *Commission Nationale d'Èvaluation des Dispositifs Médicaux et des Technologies de Santé* ("**CNEDiMTS**"), as a subgroup of the *Haute Autorité de Santé* ("**HAS**")[37], is the medical device evaluation committee in charge of technical evaluation. It is a 22-member committee that examines issues relating to the evaluation and proper use of medical devices and health technologies, including digital medical devices and informs public authorities on reimbursement decisions. The evaluation concerns the eligibility criteria defined in the March 2023 Decree necessary to assess the potential of technology: DMN must be innovative, specifically regarding clinical benefit and the progress of the healthcare system. Furthermore, the device must have the CE marking in the claimed indication. CNEDiMTS also requires the technology to be subject to ongoing trials, which are presumed to provide sufficient data for CNEDiMTS to assess, in a second step, the device for entering the LPPR. At the same time as the CNEDiMTS assessment, the device must also be evaluated by the *Agence du Numérique en Santé* ("**ANS**") to obtain the certificate of conformity to the interoperability and security standards.

The eligibility criteria are evaluated both by CNEDiMTS and the ANS within 60 days. In addition, the Ministry of Health's permission must be obtained to proceed with the process. This process can take a maximum of 30 days. Therefore, a maximum of 90 days may be required to assess access requirements.

If all the requirements are met, the DMN can enter the PECAN process for a one-year period (not renewable), reimbursed at a fixed price. Within six months from the date of inclusion in the PECAN process, the manufacturer must require product inclusion in the LPPR list. This is followed by the evaluation and price negotiation by the Ministry of Health's CEPS committee, which takes six more months. Once the evaluation phase has concluded, the product can enter the routine reimbursement phase through the Ministry of Health, reimbursed by the social health insurance. Once listed, the device will not always be fully refunded. Still, depending on the product type, it may only be partially refunded. Products qualified for reimbursement in LPPR are listed for 5 years, with the possibility of renewal.

6.3. Italy

In Italy, the term DTx was first used in 2019 in the publication 'Digital Therapies, an opportunity for Italy'[38], the first Italian document on digital therapeutics. In the following years, projects and conferences promoted the discussion on research, reimbursement, and governance of DTx, leading to a particular popularity and attractiveness. However, only recently have concrete steps been taken to enable Italy to take advantage of these innovative digital treatment options. To date, there is no specific legislative pathway for digital therapies. From a regulatory point of view, digital therapies, as they are technically software, are considered medical devices and are subject to the EU medical device regulation rules. Consequently, the route to market must provide for their CE marking.

A new opportunity for healthcare innovation is now rising in Italy. In recent months, several bodies have turned their attention to digital therapies, and the explosion of these initiatives seems to make the market entry of these technologies more concrete. From this initial overview, an absolute regulatory vacuum must be filled to fully realise the integration of pDMD into the Italian healthcare system and make these products prescribable and reimbursable.

At the beginning of 2023, a National Agency for Digital Health and Digital Therapies was set up to draft a law by 2025 to better regulate the sector and make digital therapies usable.

In addition, the National Agency for Regional Health Services ("**AGENAS**") has been tasked with defining a dedicated and accelerated HTA pathway for digital therapies. This may allow technologies to enter the healthcare system through an "HTA fast track". In addition, AGENAS will chair the Evaluation Committee, which will provide preliminary guidance on the pDMDs to be included in the HTA Fast Track to determine their inclusion in the Essential Levels of Care ("**LEA**"). The pDMDs analysed and selected will be included in the LEA update track at the Ministry of Health.

In this first phase, some basic requirements for access to the pathway reserved for digital therapies are assumed. All the information needed for the evaluation process will be collected in a structured dossier containing technical, clinical, methodological, and legal information. Following the example of other countries, it is considered necessary to carry out at least two clinical studies per device. The product must be CE-certified and must comply with the efficacy and interoperability requirements set for MDSWs.

To ensure the best conditions of use, the protection of patient health and the real integration of pDMDs into the national health system, it is essential to change the general governance of MDs, which currently does not provide for specific treatment of digital medicine products, and it is also necessary the creation of a reference body to monitor the production, fair use, and appropriateness of use of these devices.

To date, in Italy, there are already devices that meet the criteria to be defined as digital therapies, and many established companies and start-ups are working to obtain medical device certification or to structure clinical trials for their devices.

7. Policy Recommendations

Despite the potential to improve people's health, the widespread adoption of digital therapeutics has to face several challenges and barriers that limit the ability of healthcare professionals and healthcare organisations to integrate these new technologies into their care protocols.

- **Developing a joint Pre- Certification Pilot Program or Sandbox.** This shall facilitate the EU and India to jointly develop healthcare innovation in digital therapeutics. It shall assist them in understanding the requirements for defining and classifying digital therapeutics. It shall also assist the EU and India in aligning clinical evaluation requirements to ease the import-export of digital therapeutics between India and the EU.[39]
- **Fast Track Route for Digital Therapeutics.** As is already prevalent in Germany, providing fast-track approval for digital therapeutics is essential. This is important because the life cycle of software is approximately five years. The software launch becomes commercially unfeasible if the studies and approvals take 2-4 years.

- **Shared definitions.** This has started to be addressed with the publication of the ISO of DTx in June 2023.[40] Taking into account the ISO definition, the national documents (first and foremost, the draft laws) will have to provide operational guidelines that consider, among other things, the criteria for qualifying software as a DTx, the modalities for certifying a medical device, the modalities for demonstrating clinical benefit and the need for a medical prescription.
- **Shared regulatory frameworks, requirements and standards to reduce** fragmentation at the EU level, e.g. by i) defining the minimum content of the dossier, including a margin of flexibility for minor technical changes; streamlining the evaluation and process, including early dialogue between the manufacturer and the competent Authority; introducing procedures that allow immediate financing and subsequent re-evaluation by the competent Authority following the acquisition of further real-world evidence may also be considered, following the example of Germany's fast track. [41]
- **Clinical trials**. It will be necessary to clearly identify the technical-scientific requirements of the clinical trials necessary for the evaluation, approval, and financing of DTx, avoiding duplications concerning studies conducted at the international level and guaranteeing certain evaluation times by the ethics committees. Promoting the use of digital solutions of the decentralised model (DCT - Decentralised Clinical Trial) will also be relevant. Finally, it will be necessary to define the list of 'minor' changes (i.e., with no impact on the safety and efficacy of the DTx), which, if made, do not require new clinical trials.
- **Synchronisation of reimbursement pathways within the EU.** It will be fundamentally important to address issues underlying reimbursement and funding mechanisms to provide a steady, transparent path to market for digital breakthroughs. It is vital to determine value-based care for reimbursement of digital therapeutics to ensure sustainable software is promoted.[42]
- **Data management** to pragmatically balance the legitimate need to ensure patient privacy with the need to make data available for research and innovation. It is also essential that the data storage and transmission are designed so that data is available in an interoperable format.[43] This is especially important for digital therapeutic products that transmit data to healthcare providers for decision-making. Further, it is important to allow the use of anonymised, aggregated data for research and predictive analysis.
- **Accounting for Cultural Differences.** Digital therapeutics combine treatment or alleviation of a disease with cognitive behaviour therapy to improve consistency and thereby enhance treatment outcomes. This facet of digital therapeutics requires evaluation of the psychological aspects of the medical device in addition to the physiological impact. Further, the efficacy of the DTx may be impacted by cultural aspects, which need to be accounted for in designing clinical trials.
- **Training** of healthcare professionals to ensure that patients/carers are adequately informed about all the possibilities offered by digital health and training of patient experts in digital health technologies. Patients, healthcare professionals, suppliers, and manufacturers must be informed by policymakers that digital technology will play a significant role in the delivery of healthcare in the future.

Creating an ad hoc term for DTx or other pDMDs in the **European Medical Devices Nomenclature** (EMDN) could be a first measure to unlock future policy for reimbursement.

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[43] Based on primary research interviews with experts

8. Appendix

APPENDIX 1

LIST OF INTERVIEWEES

Annex/Appendix 1

List of Interviewees

SN	Countries	Interviewees	Designation
1.	Germany	Prof. Dr. Hajo Zeeb	Department of Prevention and Evaluation, Leibniz Institute for Prevention Research & Epidemiology-BIPS, Germany
2.		Dr. Leonard Fehring	Digital Health Researcher, Witten/ Herdecke University, Germany
3.		Laura Maass	PhD Candidate in Digital Public Health, University of Bremen/Leibniz Science Campus Digital Public Health Bremen
4.	India	Dr. Sudarshan Jain	Secretary General, Indian Pharmaceutical Alliance, India
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