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*Digital Therapeutics: An Ongoing Revolution**

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ABSTRACT This article deals with the much-debated topic of digital therapeutics. Starting from a general overview of the role that technology has carried out in the medical field since first innovations, this paper means to highlight the essential support that technlogy has provided, especially during the Covid-19 pandemic, which has made evident the necessity or, at least, the possibility of rethinking medical science in a more digital perspective. This article is aimed to focus on digital therapeutics, which is a specific type of technological product (such as gadgets and medical devices), highlighting remarkable differences that exist within the nebulous world of digital health, starting from the need for digital therapeutics to be supported by a clinical trial that proves its efficiency.
Moving on to the different types of diseases that can be treated, we can mention some concrete examples of digital therapeutics: Deprexis and ReSet, a cognitive-behavioral therapeutics, and Endeavor, an interactive game. In order to understand the substrate on which digital therapeutics is inserted, it is mandatory to address the issues of global regulation of this kind of therapies. Starting from the US context, in which digital therapeutics was born and authorized for the first time by the Food and Drug Administration, we reach the EU case, in which few countries are open up to this technology: in this regard, we mention the experiences of Italy, Germany, Belgium, France and England. In the end, the article examines the critical issues and potential that digital therapeutics represent for health systems.

1. *Digital Therapeutics: a new frontier for modern medical science*

Medical science has always represented a challenging test bed for technology which, from time to time, brings into play solutions ranging from the improvement of services to the optimization of treatment pathways, from the reduction of the adverse effects of treatments to de-hospitalization. In particular the research for new therapies, aimed at treating pathologies previously considered incurable or at reducing their side effects, is the area where the efforts of pharmaceutical companies have been most concentrated on, which over the decades have revolutionized existing therapies: we can take into consideration the marketing of biological drugs first and then of genetic therapies, i.e. drugs whose therapeutic effect is determined by an active ingredient that is no longer of synthetic but biological origin, made up of recombination of genes.

The introduction of these therapies inevitably has changed the way of doing research in the health sector, opening the door to a whole series of hitherto unexplored possibilities. It is, as a matter of fact, thanks to this that, in recent years, the "technological need" of health systems has grown exponentially, in parallel with new clinical discoveries and above all, lastly, with the need to deal with the Covid-19 pandemic, which has seriously put to the test health services globally: these phenomena have once again highlighted the therapeutic potential of technology, capable of guaranteeing greater safety and continuity of treatments even in complex and uncomfortable contexts. It is thus on this substrate that we have witnessed the development of the first digital therapeutics, concerning which the international debate is very lively and much confusion still prevails.

The Digital Therapeutics Alliance states that "digital therapeutics (DTx) delivers medical interventions directly to patients using evidence-based, clinically-evaluated software to treat, manage and prevent a broad spectrum of diseases and disorders". In other words, it is an application of the so-called Digital Health which is expressed in a real cure delivered through the active role of technology, which is no longer conceived as a mere support for pharmacological therapy, but as the main or single treatment. This statement is already indicative of the revolutionary scope of Digital Therapeutics, whose active principle is not a molecule, as in the case of pharmacological therapies, but an algorithm that structures the treatment that the patient must undergo on the basis of the information provided by the doctor or by the patient

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himself or herself.

If, DTx undoubtedly falls within the great category of Digital Health, as highlighted above, it is however not easy to understand what is meant by this term.

First of all, outside the scope of Dtx are all those devices aimed at simplifying and enabling the very delivery of services,[1] those applications having a patient-information function as well as all AI and robotics applications used at the clinical level.[2]

Likewise, cannot be considered DTx all those technological gadgets (Mobile Health) that are intended to ensure and manage the monitoring of vital parameters, which are supported and screened by clinical trials solely prior to the placing on the market[3] and lacking such characteristics to act in itself as a therapeutic treatment.[4]

Above all, on the other hand, attention must be paid to the distinction between DTx and medical devices, which are the subject of experimentation and clinical validation and are able to measure and intervene on the patient's health, but in a purely auxiliary function. These devices, in fact, are characterized by the support that technology offers in the prevention, management and treatment of the pathology, without it representing an essential element of the cure. This distinction between medical devices and DTx is not so intuitive, as clinical-trial data on the subject show.[5]

Therefore, to summarize the elements that distinguish DTx from other Digital Health applications, the following aspects can be highlighted:

- Digital therapeutic treatment (monotherapy or in combination) based on software as an active principle;
- Validation of the efficacy of the treatment following a clinical trial in 4 phases (preclinical phases of research and discovery; clinical phase with clinical development pilot and subsequent clinical development pivotal; submission; post marketing surveillance phase);
- Authorization from regulatory bodies, such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA, for the centralized authorization or mutual recognition procedure) or national bodies (e.g., AIFA, BfArM, NICE, etc.);[6]
- Medical prescription and possibility of reimbursement by the health system.

As can be guessed, some of these elements are also common to other Digital Health applications (e.g., Telemedicine prescribing or the authorization process for medical devices): the main difference is that only an application that simultaneously meets all of the above requirements is considered DTx.

2. *Digital Therapeutics scope and examples*

Once analyzed the context in which DTx is inserted, it is now necessary to analyze its perimeter, i.e. to understand which pathologies can concretely be treated through the administration of digital therapies. Indeed, the latter obviously cannot be prescribed either whenever surgery is necessary or for diseases and conditions in which the patient's compliance has a limited role (think of the case of a fracture to the femur or removal of a tumor mass). Otherwise, DTx tends to prefer those pathologies that require long-term therapeutic-assistance pathways for which the administration of a drug can be replaced, hence mainly chronic, psychological or central-nervous system pathologies.

Towards these pathologies, digital therapeutics' approach may be implemented in various ways, starting from the preparation of a cognitive-behavioral therapy which provides for the active involvement of the patient, seeking the implementation of

[1] Think in this regard of apps or digital services for booking services or consulting reports.

[2] This includes Telemedicine (in all its forms: telemonitoring, telehealth, teleconsultation, telerehabilitation, etc.), surgical robots and nanorobotics.

[3] The main difference between clinical trials related to Mobile Health and Digital Therapies is that the latter are also subject to Real World Evidence, i.e., verification of effects and outcomes in medical practice following authorization and marketing.

[4] Examples include smartwatches, smart bracelets, sensors that can detect ingested medications, etc. Thus, these are useful tools for human-health management, yet they are a support and not a therapy.

[5] As reported by Professor Eugenio Santoro during the webinar *Terapie Digitali: dallo sviluppo alla pratica clinica. Una rivoluzione possibile*, held by the Osservatorio Terapie Avanzate on 14 October 2022, many studies on digital therapies were subject to review and exclusion once it was ascertained that they were merely observational studies or experiments relating to mere-support tools. Out of 560 studies considered, as a result of these reviews, only 136 actually resulted in DTx.

[6] Thanks to their nature as a therapeutic treatment, hence, digital therapeutics are subject to a process of research, experimentation and authorization for prescription and marketing similar in terms of timing and regulation to that envisaged for any other drug.

corrective behaviors and/or of one's own situation.

Precisely committed to this purpose is Deprexis, the first digital therapy approved in the world in 2009, created by the Gaia company. Deprexis was developed in Germany for the treatment of what is estimated will be the most common disease in the world by 2030: depression. The basic algorithm of Deprexis is structured in order to provide a 12-week cognitive-behavioral therapy (CBT) as an alternative to the traditional psychological/psychiatric path: the platform is actually able to interact with the patient as a real therapist, analyzing the answers provided with the aim of returning a personalized therapeutic path available 24 hours a day, 7 days a week, on any technological device.

The basic idea of Deprexis was subsequently taken up and developed, among others, by ReSet, authorized by the Food and Drug Administration (FDA) in 2017 as the first DTx in the USA. Marketed by Pear Therapeutics, undisputed leader in the research and development of digital therapeutic area, ReSet was created for the treatment of addictions in the form of an app.[7]

The standard treatment provided for substance dependence (alcohol, smoking, drugs, etc.) takes the form of a multi-professional approach involving different roles (psychologists, psychotherapists, psychiatrists, educators, social workers, etc.) and includes rehabilitation programs in dedicated structures or structured with the aid of therapies, whether pharmacological or rehabilitative. On the other hand, through the insertion of data (e.g. those relating to craving, i.e. the impulse to take substances) that influence its algorithm, ReSet returns a cognitive behavioral therapy lasting 12 weeks, with a recommended dosage of 4 "doses" per week. The digital treatment the patient[8] accesses is represented by interactive lessons, feedback, advice, corrective exercise of their habits modules which are designed precisely on the basis of the information provided by the patient, who also always has the possibility of requesting medical assistance. Furthermore, not only might ReSet be prescribed for the outpatient treatment of addicted patients, but it is also constantly subject to the supervision and monitoring of a clinical professional, who also has the possibility of repeating the treatment prescription, whenever necessary to continue for a period longer than 12 weeks. The structuring of the treatment proposed by ReSet makes it suitable for use as a standalone (monotherapy) or plug-in treatment, i.e., as a support and enhancement to the pharmacological / psychological treatment.[9]

Conversely, Akili Laboratories adopted a total different approach beyond the creation of Endeavor, DTx authorized in 2020 by the FDA for the treatment of children between 8 and 12 years of age suffering from Attention Deficit Disorder with Hyperactivity (for short "ADHD").[10] Endeavor has entered this context using the Akili Selective Stimulus Management Engine (SSMETM)[11] technology, designing an interactive-action videogame customized according to the

[7] A later version, ReSet-O, is specifically aimed at the treatment of opiate addiction.

[8] At present, ReSet is only prescribable to patients over 18 years of age.

[9] The potential of ReSet was immediately evident and also confirmed by studies, such as the randomized one carried out on 507 patients for a duration of 12 weeks, in which people were divided into 2 groups according to whether they used the "classic" treatment or ReSet[9]: the study returned the photograph of a strengthened compliance of the patients to whom ReSet had been prescribed compared to those who had benefited from a face-to-face psychological treatment path. This positive outcome can be traced back to various factors, among which undoubtedly stands out the major responsibility of the patient, who is directly involved as a partner in the treatment and not as a passive subject, and the possibility of using this treatment in any place and at any time, ensuring greater privacy compared to the social stigma that often characterizes addiction treatment. To learn more about this, see A. Biondino, *Arriva ReSet, l'app per curare le dipendenze*, in *Nurse Times*, August 2018 (*https://nursetimes.org/arriva-reset-lapp-per-curare-le-dipendenze/54670*), and *Se il medico prescrive un digiceutico*, in *About Pharma*, January 2019, via *www.aboutpharma.com/blog/2019/01/30/se-il-medico-prescrive-un-digiceutico/*

[10] The symptoms of ADHD are mainly inattention, impulsivity and easy distractibility, thus affected children and adolescents show greater difficulty in maintaining concentration and completing assigned tasks; for these reasons, although there are different approaches in the USA and Europe, the recommended treatments for this disorder range from pharmacological therapy to behavioral therapy.

[11] R. Ascione, M. Beccaria, S. Grigolo, G. Gussoni, N. Martini, E. Santoro, A. Ravizza, G. Recchia and V. Rosso, *Digital Therapeutics dalla A alla Z – Storie di Digital Therapeutics - Endeavor*, in *Pharmastar*, July 2020: SSMETM is "a proprietary technology designed for the targeted activation of specific neural systems in the brain for the treatment of diseases with associated cognitive dysfunction" and, therefore, "features specific sensory stimuli and simultaneous motor challenges designed to target and activate the neural systems that play a role key in the function of attention".

characteristics and needs of the individual patient, who must maintain the necessary concentration to achieve objectives and avoid obstacles in order to pass one level after another.[12] This particular element of innovation represents the better effectiveness compared to the classic-educational video games in the treatment of this disorder.[13]

In other words, Endeavor falls within the category of so-called "serious games" and its digital treatment is based on the principle of "gamification"[14] i.e. the administration of an engaged interactive video game which is not perceived by the patient as an imposition or a treatment. Nonetheless, it allows the pursuit of health objectives guaranteeing the involvement and even the enjoyment of the patient.

Among the 36 DTx that have been authorized in September 2022 globally,[15] with a clear predominance of the USA in this sense, Endeavor represents one of the few interactive video-game experiences. On the other hand, the cognitive-behavioral therapies structured in the form of apps in the light of ReSet are more consistent, since they come out more easily suitable to various pathologies (depression, hypertension, diabetes, sleep disorders and insomnia, anxiety disorder, obesity, smoking addiction, etc.).

3. *American and English regulation of Digital Therapeutics*

The undisputed innovative scope of digital therapeutics is indeed the most interesting aspect of these technologies, but also one of the reasons of greatest difficulty for national legislators. As a matter of fact, considering the position taken by individual States in terms of DTx, we are witnessing a real regulatory patchwork.

As far as concerned, it is certainly not surprising that the USA, pioneer in terms of technology, is also the most open country to digital-therapeutic regulation. Since the trade authorization of ReSet in 2017, the FDA has in fact gradually taken on an increasingly proactive approach towards the issue and, with its Digital Health Software Precertification Program[16], has prepared a scheme of approval of the DTx, describing which requirements the interested companies must demonstrate to possess (e.g. an advanced level of security in the management of personal data, a robust quality management system, etc.) and the phases of the approval procedure.

The Digital Health Software Precertification Program, launched in a pilot version in 2017 and completed in September 2022, is joined by the Federal Health IT Program for 2020-2025, which provides the development of a plan for the use of scientifically-validated Digital Therapeutics for the prevention, treatment and management of various pathologies.

The real problem that the USA is facing in relation to DTx is its reimbursement, which, in the absence of a universal or mutual-health system, is left to the discretion of the system. In principle, access to these treatments is actually subject to payment from the user. However, in parallel with the increase in clinical-scientific evidence relating to the effectiveness and efficiency of DTx, there are more and more initiatives by insurance companies aimed at including digital solutions within their portfolios to reduce the hospitalization rate (and re-hospitalization) and the risk profile of their customers. In addition, several companies have also begun to offer digital therapeutics to their employees as a form of corporate welfare. Therefore, it can reasonably be said that this trend will continue to grow in the coming years.

Simultaneously, it is also noteworthy the experience of United Kingdom, whose National Institute for Health and Care Excellence (NICE), in 2018, published some

[12] Game performances - which should include 25-minute sessions to be repeated/5 times a week for at least 4 weeks according to instructions - are recorded by the system and used to return a as-customized-as-possible experience.

[13] As demonstrated by the various studies used for the release of the authorization by the Food and Drug Administration and subsequently published. To deepen, see also S.H. Kollins, D.J. DeLoss, E. Canadas *et al*, *A novel digital intervention for actively reducing severity of paediatric ADHD (STARS-ADHD): a randomised trial*, in *Lancet Digital Health*, 2020.

[14] G. Riboli and V. Alfieri, *L'utilizzo dei videogiochi per una terapia più efficace del Disturbo da Deficit di Attenzione e Iperattività (ADHD)*, in *Lo psicologo del futuro*, n. 12, July 2021.

[15] Source R. Mazzaracca and E. Santoro, *Terapie digitali approvate: a che punto siamo e quali sono?*, in *Advanced Therapy Observatory*, March 2022 (*www.osservatorioterapieavanzate.it/innovazioni-tecnologiche/terapie-digitali/terapie-digitali-approvate-a-che-punto-siamo-e-quali-sono*).

[16] P. Taylor, *Better Therapeutics files for FDA approval of diabetes DTx*, in *Pharmaphorum – bringing healthcare together*, September 2022.

guidelines[17] aimed at ensuring that digital therapeutics be clinically validated, effective, and able to offer economic benefit. These guidelines, revised in 2021, intend to identify the most appropriate levels of evidence depending on the device required by NICE; it should be pointed out, however, that any NICE approval does not automatically allow for reimbursement by the English healthcare system, although it undoubtedly gives support in this regard. To date, the applications Deprexis (for the treatment of depression) and Sleepio (for insomnia[18]) are the two DTx that have obtained NICE approval and reimbursement from the National Health System (NHS).

4. *The regulation of Digital Therapies at the Italian and European levels*

Meanwhile, the situation in the Old Continent is more complex, the regulatory framework is traced by EU Regulation 2017/745 of 5 April 2017 concerning medical devices, which repeals and replaces directives 90/385/EC[19] and 93/42/EC.[20]

This regulation aims to ensure the proper functioning of the internal market for medical devices and a high level of safety of the same and protection of patients' health;[21] analyzing the regulatory text, it can be seen that the European legislator intended to regulate in a single text the regulatory procedures, functional to the evaluation and reimbursement, regardless of whether they relate to medical devices or digital therapeutics.

Indeed, the Regulation apparently brings software used as therapeutic treatment - that is, precisely, digital therapeutics - back within the definition of medical device, which is mentioned both in Article 2[22] as well as in Recital n. 19.[23] This leads one to believe that the heading of the Regulation should be understood in an atechnical sense, whereby it regulates medical devices and digital therapeutics, without dwelling on the intrinsic differences existing between these two categories of technological-health applications, as previously analyzed. In addition, it is pointed out that Article 1 (VI) of Eu Regulation 2017/745 does not expressly include digital therapies within those devices, medicines and materials to which the regulations therein cannot be deemed applicable.

After all, it is the Regulation itself, in Recital No. 8, that provides for the possibility of borderline or otherwise doubtful cases, stipulating that it is up to the Member States to decide on a case-by-case basis whether such devices are subject to the discipline provided therein.

This impression is also confirmed by MDGC 2019/11 (Guidance on Qualification and Classification of Software in Regulation EU 2017/745 - MDR[24]), guidelines prepared by the European Commission for the correct application, precisely, of the Medical Device Regulation (MDR) at the European level. Indeed, while it is true that the Regulation includes software within medical devices, at the same time it does not seem to expressly

[17] This is the Evidence Standards Framework for DHTs, easily reachable on *www.nice.org.uk/about/what-we-do/our-programmes/evidence-standards-framework-for-digital-health-technologies*.

[18] Based on more than a dozen randomized trials submitted to NICE, Sleepio has not only been found to be a viable clinical alternative to classical pharmacological treatment against insomnia, but has also been shown to reduce the direct and indirect costs caused by this condition on the health-care system. This lower economic impact is due to the cognitive behavioral therapy provided by Sleepio as an alternative to pharmacological treatment, which involves recurrent expenses for the purchase of medications and follow-up visits. On the point, R. Mazzaracca, *Trattare l'insonnia con un'app: in UK è realtà*, in *Osservatorio Terapie Avanzate*, giugno 2022, e R. Ascione, *Digital Therapeutics dalla A alla Z - Un mondo a velocità diverse*, in *Pharmastar*, July 2020.

[19] Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices.

[20] Council Directive 93/42/EEC of 14 June 1993, on medical devices.

[21] As reported by Recital n. 2 of the EU Regulation 2017/45, "both objectives are being pursued simultaneously and are inseparably linked whilst one not being secondary to the other".

[22] Art. 2 of the EU Regulation defines medical device as "any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination" for the various medical destinations specified.

[23] Recital n. 19 of the EU Regulation explains that "It is necessary to clarify that software in its own right, when specifically intended by the manufacturer to be used for one or more of the medical purposes set out in the definition of a medical device, qualifies as a medical device, while software for general purposes, even when used in a healthcare setting, or software intended for life-style and well-being purposes is not a medical device. The qualification of software, either as a device or an accessory, is independent of the software's location or the type of interconnection between the software and a device".

[24] In fact, these guidelines also cover EU Regulation 2017/746 on in vitro medical devices.

contemplate the possibility that any therapeutic effect derives from them. In other words, the inclusion of digital therapies within the discipline of medical devices derives from a broadly-oriented interpretation of the term "software".[25]

This inherent ambiguity explains the different speeds and propensities with which Member States have read to concretely apply the Regulation, which entered into force at the European level on 25 May 2017.

4.1. *The Italian experience*

As far as Italy is concerned, for example, the transposition of EU Regulation 2017/745 was supposed to take place within the three-year period following its entry into force, but the Covid-19 pandemic postponed that time by an additional year, making it de facto fully applicable only from May 26, 2021. The problem that was immediately noted, however, lies precisely in the apparent ambiguity of the text, which does not expressly mention Digital Therapies: hence the uncertainty of the domestic legislature in assigning responsibilities to the Ministry of Health or to the Italian Medicines Agency (AIFA). In fact, if, as the Regulations let it be understood, Digital Therapies are to be regulated in the same way as medical devices, they would fall under the competence of the Ministry of Health (Department of Drugs and Medical Devices); on the contrary, were Digital Therapies to be considered drug-therapies, the competence should be avocated to the AIFA as the country's public regulatory body able to authorize them. Until June 2023, no internal legislation had resolved the doubts on the matter, which are reflected in the clinical validation and reimbursability modalities; nonetheless, the legislative proposal submitted on June 7, 2023 to the Chamber of Deputies, specifically titled "Provisions on Digital Therapies," clearly states that DTx is classified as medical devices, in line with European regulations.

Moreover, the aforementioned legislative proposal -currently under consideration by Parliament -represents the first real evidence of awareness of the importance of digital therapies not only for progress but for the very survival of the Italian health care system as well, which has been severely undermined by the repercussions of the Covid-19 pandemic. Structured in 4 articles, the legislative proposal analyzes the possible repercussions that would result from the introduction of DTx in the Italian system: in this regard the law proposes the establishment of an evaluation committee in charge of ensuring a fast track for inclusion in the essential levels of care (so called "LEA"), flanked by a permanent observatory deputed to monitoring and updating the scientific and technological developments of these therapies.[26]

Awaiting regulatory intervention, despite the strong push for technological innovation registered in the last two years due to the pandemic, the diffusion of digital therapeutics in Italy is literally paralyzed: to date, in fact, no DTx has ever been authorized for trade and prescription in the country. In this regard it should be considered that, since Regulation 2017/745 includes software among medical devices and several DTx are already authorized in other member states, a certification to that effect from the Ministry of Health or the Italian Drug Agency would be sufficient for their marketing and reimbursability.[27]

In early 2023, however, the Ministry of Health authorized the start of the Demetra clinical trial, which aims to evaluate weight loss in patients using the new DTxO, involving two Italian health institutions (Istituto Auxologico Italiano and Policlinico Giovanni Paolo XXIII in Bari). "DTxO" is in fact an app designed to treat patients with obesity on an outpatient basis. With a nonpharmacological approach, DTxO provides digital treatment on two levels: on the one hand, it offers dietary plan and patient education/support (dietary and exercise advice program, cognitive-behavioral assessment program, alerts and warnings, chat and televisite); on the other hand, to ensure good patient retention, it is structured in the gamification mode. Hopefully, therefore, Italy

[25] The uncertainty that characterizes the Regulation on the point also makes complex and dangerous the correct risk classification of digital therapies within the categories of medical devices provided and differentiated according to their impact on human health and, therefore, risk. See *Digital therapies, an opportunity for Italy*, in *Tendenze Nuove*, L. Da Ros, G. Recchia, G. Gussoni et al, January 2021, pp. 17-27.

[26] See www.camera.it for the legislative proposal.

[27] It is due to the fact that the verification about the safety and efficacy of these products would already be carried out. On this point also C. Buonamico, *Digital Health and Digital Therapeutics: where are we?,* in *Policy and Procurement in Healthcare*, August 2022.

will also see the first marketing of a digital therapy in the medium term.[28]

In the same vein is the "Digital therapeutics for Obesity", a 2019 project coordinated by the University of Verona and the company DaVinci Digital Therapeutics having as its object the development - by means of a pilot study - of a digital therapy for the treatment of obesity, which is estimated to affect one in ten people in the country. The project, which is still in progress, involves the creation of software capable of monitoring parameters entered by the patient and/or recorded by wearable devices and returning activities to be performed and feedback from the multidisciplinary health team deputed to the patient's care.

Additionally, then, there are notable initiatives, aimed at raising stakeholder awareness of the importance of digital therapies for medicine in line with the clinical, organizational and economic needs of the moment.

Among these, there is the Smith Kline Foundation's "Digital Therapies for Italy" project, which from July 2019 to December 2020 has involved a panel of experts in order to deepen the necessary requirements for the introduction of digital therapeutics in the country. The working group - which has grown over time from the original 21 members to more than 40, representing different technical expertise functional to a fruitful debate - has produced a document[29] that analyzes both the stages of digital-therapeutic development and the stages of introduction into care pathways. Thus different aspects have been examined: the research and development models, the level and nature of evidence of efficacy and tolerability of a digital therapeutic; the terms and criteria for evaluation by regulatory entities as well as for reimbursability; the modalities for the integration of such therapies in medical practice; finally, the conditions to allow Italy to be a user country, but more importantly to join the roster of research countries.

Finally, it must be considered remarkable Vita Acceleratorm, a three-year funding program, which in 2022 selected 6 start-ups engaged in the Digital-Health field – among 120 applications - in order to support the development of both Digital-Medicine and Digital-Therapeutic solutions. Among the start-ups that will benefit from the €6.35 billion fund made available by Vita Accelerator is Sifi, an Italian pharmaceutical company committed to the study of eye diseases and now interested in the creation of a digital therapy for the treatment and maintenance of vision.

4.2. *The European context*

Conversely of a different tenor is the experience of Germany, which is undoubtedly the most active European country in DTx. The turning point came in 2019, when, in the wake of EU Regulation 2017/745, the Bundersat officially adopted the Digitale Versorgung Gesetz (DVG) approved by the Bundestag. Indeed, the DVG paved the way for clinicians to prescribe - often electronically - Digital Therapeutics and specifically medical apps by regulating their reimbursability by private-insurance companies, which are the payers of the German mutual system. To facilitate manufacturers and incentivize them to invest in digital innovation, the German Federal Institute for Medical Devices (BfArM) has devised a pathway structured as follows:

- BfArM approval following clinical-functional validation of digital therapeutics (or DiGA, as it is called in Germany) from the perspective of safety, data protection, functionality and quality;
- Temporary reimbursability for the next 12 months;
- New validation by the BfArM for which manufacturers must demonstrate the app's improved impact on patients' health. Whenever such proof is achieved, the app becomes officially and permanently reimbursable by the health-care system; otherwise, the application for reimbursability cannot be resubmitted.

The fast-track described above is not applicable to any type of DTx, but only for the less hazardous devices, falling in classes I and

[28] The Demetra clinical trial covers a time frame of about 18 months: once eligible patients (adults aged 18 to 65 years, with a BMI between 30 and 45 kg/m2) are identified, 250 will be enrolled and undergo a 12-month observation period following the first visit. During this time frame, there will be a weight loss check after 6 months and a subsequent verification of further weight loss and/or maintenance of weight achieved at month 12. On this point see *DTxO, from Theras Lifetech and Advice Pharma the first digital therapy for the treatment of obesity*, via *www.advicepharma.com*

[29] Here again the reference is to *Terapie digitali, un'opportunità per l'Italia*, in *Tendenze Nuove*, L. Da Ros, G. Recchia, G. Gussoni *et a*l, *ut supra*.

IIa;[30] insofar, neither those belonging to the higher risk classes, which will therefore undergo a more rigorous pathway, nor those that do not have medical characteristics or that perform a mere support function regarding the therapy are included among the devices that benefit from reimbursement.[31]

The path initiated by the DVG aims to enable an ever-widening range of beneficiaries to benefit from the prescription and reimbursability of DiGAs, with an investment in digital-health innovation of €200 million per year until 2024[32] and more than 500 DiGAs submitted for BfArM approval as of March 2022, of which 21 are officially authorized and reimbursed.[33]

As for the rest of the European Union, several countries are following in Germany's footsteps. First among them was Belgium, which, in February 2020, formed an internal working group at the National Institute for Health and Disability Insurance (NIHDI) for the development of DTx reimbursement procedures. The outcome of that study is the so-called mHealth validation pyramid,[34] which presents all the requirements that the digital therapeutics being evaluated must possess, namely:

- Compliance with CE mark and EU Data Protection Regulation 679/2016 (GDPR), with assessment by the Federal Agency for Medicines and Health Products (FAMHP), belgian pharmaceutical regulatory body;
- Adequacy of the digital device in terms of data security and confidentiality, connectivity and interoperability;
- Clinical and socioeconomic demonstration of the added value of DTx over ordinary treatment.

If the therapy being evaluated passes all the steps in the mHealth pyramid, NIHDI provides for its reimbursement by insurance companies. To date, 34 digital therapies have achieved reimbursability in the country through this system.[35]

Finally, France is also showing some interest in Digital Therapeutics. Inspired by Belgium, France is drawing its attention to the requirements that DTxs must meet in order to obtain certification and reimbursability at the insurance level,[36] but with the aim of still ensuring a German-inspired fast-track. The French regulations will come into full effect by the end of 2023, but as of today Insulia, a DTx manufactured by Voluntis for the management and treatment of type II diabetes, is already on the official list of reimbursable health products and services.

5. *Future prospects: potential obstacles to development*

What has been analyzed so far allows us to draw an initial assessment of the impact of digital therapies on health systems, starting from the fact that almost everywhere there is a growing interest in this new type of treatment. Nonetheless, in order to understand the reasons underlying the slowness and/or distrust in the implementation by some States and to promote awareness of the benefits associated with these devices, it is necessary to pinpoint the barriers to development that exist today.

First of all, the absence of clear and shared legislation on the subject represents a gray area that is not entirely insignificant, since the regulation of processes and standards is left to the individual States and this leads to great fragmentation, differences in discipline and often also increases costs and development delays. In Europe this obstacle could be bypassed, for example, with the adoption of a centralized approval process such as to make transposition in the individual Member States more streamlined and automatic.

Secondly, the aforementioned regulatory fragmentation is also reflected in the absence of precise guidelines on reimbursement. This certainly represents the greatest barrier, because it is unimaginable ad unacceptable to think of the approval of any digital therapy in the absence of the relative reimbursement: in

[30] The combination of UE Regulation 745/2017 art. 51 and Annex n. VIII resumes and partially modifies the distinction between medical device risk classes already regulated by the Directive 93/42/EEC.

[31] M. Roehl, *DiGA – Digital Therapeutic Health Application*, in *Allied Clinical Management*, March 2022: "to be defined as a DiGA in Germany it cannot be used exclusively to collect data from a device or for controlling a device, thus it must be used to support the recognition, monitoring, treatment or alleviation of disease or the recognition, treatment or alleviation or compensation of injuries or disabilities".

[32] Source: Federal Ministry of Health, via www.bundesgesundheitsministerium.de/en/digital-healthcare-act.html.

[33] M. Roehl, *ut supra*.

[34] To better understand, see *https://mhealthbelgium.be/*

[35] J. Stevovic, *Terapie Digitali (DTx): framework disponibili in Europa, UK e Stati Uniti*, in *Digital Health Italia*, August 2022.

[36] Vetted by Haute Autorité de Santé (HAS).

Italy, for example, the failure to reimburse digital therapeutics would entail the risk of creating inequity in access to equal or more effective tools, an unacceptable outcome in a universalistic system such as the Italian one.[37]

Undisputedly, all these problems track back above all to a cultural approach still linked to an old conception of medical science, which does not always prove capable of applying the available technological advances: this can be seen both in the poor knowledge of the clinical-validation procedures, which should be more widely shared to promote a full understanding of the phenomenon, as well as in the reluctance of some governments and companies to implement due to the costs and resources (technological and human) to be used in development. If this is accompanied by lack of familiarity with the technology by a part of the healthcare personnel entitled to prescribe such devices, it is easy to understand why digital therapies have not yet reached full diffusion.

Obviously, the hope is that the theoretical interest in these therapies will be accompanied by a concrete commitment to their development. As analyzed in previous paragraphs, digital therapeutics placed on the market have demonstrated clinical efficacy equal to or even superior to the corresponding therapeutic treatments, thus representing a valid alternatives or replacements especially in cases of particularly serious adverse effects or pathologies involving social stigma. Furthermore, the greater active involvement of patients in the treatment required by the therapies – whether by entering data and sending feedback, or by actively participating in games and quizzes – on one hand ensures greater responsibility, also in terms of cost of therapy, and on the other, increased compliance. This positive aspect is particularly appreciable if we consider that one of the most significant problems that apps in general are faced with is precisely the so-called retention, or the ability to retain the customer (patient in this case).[38]

Perhaps the most evident and impactful potential for health systems deriving from the use of digital therapeutics is represented by de-hospitalization: the possibility of preventing or managing a pathology with the aid of a software, which can be used on any digital device at any time of the day and in any place, allows clinicians to concretely guarantee continuity of care and treatment pathway, which is one of the cornerstones and objectives of modern medical science. This, in fact, allows to continue the treatment paths outside the structures, with a strong reduction of costs for the system, more space for acute pathologies or those that require non-replaceable intervention and a different perception of the treatment by the patients, who include it in their daily routine being able to lead a regular life outside the hospital. For this purpose, it would be desirable for individual countries to demonstrate their sensitivity on the subject, proposing courses and technological-education pathways both for healthcare personnel and, especially, for patients, in order to allow anyone actual access to these therapies, which necessarily passes through the understanding and ability to use them.[39]

Hence the development of digital therapies is not free of obstacles and risks. First and foremost, as mentioned, inadequate training of healthcare personnel can lead to counterproductive effects in the care of patients, whose course of treatment could even be slowed down and/or worsened if not properly set up and followed up.

Analogously, poor attention to cybersecurity issues could lead to serious data breaches related to sensitive data entered by/on patients. It is precisely this aspect that is of greatest concern, as evidenced by the healthcare world's focus on insurance solutions to protect against this risk in view of the increasingly-frequent attacks on IT facilities and systems.[40]

[37] In other words, if digital therapies are approved and certified as alternatives or substitutes for traditional therapeutic treatments for which the National Health System (SSN) provides reimbursement, this means that the reimbursement regime must be analogously extended to these new therapies.

[38] A 2019 *Localytis* study reports that nearly one quarter of users abandon an app after just one use and that 62% of users use an app less than 11 times in their lifetime. Source: G. Tripodi, *Un utente su quattro abbandona le app dopo un solo utilizzo*, in *Smartworld*, March 2019.

[39] We are therefore linked to a concept of health *literacy* in the broadest sense.

[40] In this regard, it can be unarguably stated that, with respect to this risk, the insurance market is characterized by hard-market conditions, i.e., increasing premiums and shrinking insurance coverage capacity. This situation is mainly found as a result of the increase in the number of claims in a certain field and is indicative of the rigidity of the system, which struggles to meet the high demand due to a restricted and/or very expensive supply.

Nevertheless, both the potential and the critical issues that have emerged during the pandemic, linked to the growing needs expressed by health systems and populations, point out that the only viable path for health seems to be the one traced out by digitization: in this sense, Digital Therapeutics represents the goal to pursue.