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DIGITAL THERAPEUTICS: AN OPPORTUNITY FOR ITALY, AND BEYOND

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Executive Summary

1. Digital therapeutics (DTx) can be defined as technologies that "offer therapeutic interventions driven by high-quality software programmes, based on scientific evidence obtained through methodologically rigorous confirmatory clinical investigation, to prevent, manage and treat a broad spectrum of physical, mental and behavioural conditions". DTx can be used on a stand-alone basis or in association with other evidence-based therapeutic interventions - for example, a drug. As such, they must not be confused with the hundreds of thousands of digital applications available to citizens and patients for an enormous variety of wellness and health purposes. DTx as defined above are already authorized and available for use in some countries, subject to medical prescription and eligible for reimbursement by public health services (e.g., in France and Germany), or reimbursable by private health insurance schemes (USA). In Italy, there are currently no DTx available for prescription and/or clinical use, and/or recognized by the health service.

2. DTx are considered as medical devices, and are thus subject to the provisions of Regulation (EU) 2017/745 on medical devices, which entered into force in May 2021. However, this Regulation contains no specific provisions for DTx; and, more generally, there are some regulatory matters on which indications with a greater level of detail would be desirable (e.g., with regard to subdivision into risk classes, the approach to be taken by notified bodies concerning regulations applicable to DTx, etc.). In regulatory terms, there is thus an evident need for specific indications regarding DTx. Such indications would be particularly useful in relation to the peculiar features of DTx, such as their rapidly evolving technology and potential vulnerabilities in terms of data protection and cybersecurity.

3. Design and clinical use of DTx must factor in possible issues in relation to data protection (given the large quantity of sensitive data generated by these technologies) and cybersecurity. The reference documents in this regard are European Regulation 2016/679 (the General Data Protection Regulation - GDPR), the guidance on medical device cybersecurity issued by the Medical Device Coordination Group (MDCG, December 2019) and the International Medical Device Regulators Forum (IMDRF, March 2020). However, giving their inevitably rather general nature, these documents do not focus specifically on DTx. In particular, with regard to cybersecurity, DTx present two main vulnerabilities to attack: the cloud data store (in other words, the facility for online data storage), and the fact that the DTx app could be housed on a mobile device belonging to the user. This means that the application of high-level governance guidelines like those of the MDCG and IMDRF has to be complemented by specific, detailed technical analysis in order to produce security controls specific to DTx - for example, following a template such as that provided by the family of ISO/IEC 27000 standards.

4. Regulation (EU) 2017/745 establishes the need to demonstrate a clinical benefit of medical devices, requiring that they must be not only safe but also clinically effective. This demonstration should be obtained by clinical investigation, though the regulation provides no particular details about what the characteristics of this investigation must be. What is needed is greater regulatory detail at European level (for example, in the form of an addendum to the EU Regulation), in relation to DTx-specific clinical investigation supporting their certification and authorization for use. For a device with a therapeutic aim, this will make it possible to guarantee adequate, uniform efficacy and safety standards, similar to those for drugs used in the same therapeutic indications. While recognizing that traditional research methods for evidence collection are not systematically and by definition applicable to DTx, that the risk of obsolescence necessitates rapid lead times for DTx development, and that their peculiarities must be taken into account at the study design phase, randomized, controlled trials (RCT) are to be recommended for clinical investigation. These must be carried out on an adequately sized sample (particularly in confirmatory "pivotal" studies), so that significant effects can be statistically demonstrated. A critical future of DTx is the frequent advisability/need to update the technology, even when clinical development is ongoing. It seems

reasonable that general criteria should be defined to allow implementation of some technological updates, without this entailing the need to start the entire clinical investigation again from scratch. Specifically, *minor* modifications not entailing changes to the main architecture of the software or its intended use could be acceptable. Indicatively, and not exhaustively, examples of minor modifications could be a new user identification system (e.g., biometrics rather than a password), the inclusion of new icons in the user interface, or updates to the user's or customer assistance manual for patients and healthcare professionals. Clinical investigation must not overlook accurate assessment of any possible undesired effects that might be caused by the use of these technologies, and must also give consideration to the need for specific, local evidence in the case of DTx developed in appreciably different care, epidemiological and cultural settings. It is equally important to provide for an adequate post-marketing surveillance system in relation to DTx, enabling real-world reassessment of their risk-benefit profile. A related point of great interest regarding DTx is that, in delivering therapy, they allow continuous real-time collection of data and information, which can thus be retrieved from databanks for research purposes and for possible adaptation of the therapy; in this way, DTx can be a powerful tool for knowledge and real-world data evidence management.

5. Dissemination of DTx and their major role in care pathways are closely linked to the clinical benefit that these technologies are - and will be - able to demonstrate, but also to the related regulatory and economic setting. Given their therapeutic role, DTx should always be developed by controlled clinical investigation, enabling support for claims regarding efficacy, safety and recommended use; they should also be subject to a regulatory authorization procedure for specific therapeutic indications, with a view to their medical prescription - and, possibly, reimbursement - by the health service or by third parties. In different health and economic settings, which tend to change quickly (just as digital technologies themselves continue to evolve almost non-stop), an equally plausible scenario is one where, in the same way as for drugs, self-prescription could also be envisaged: in any case, for products to qualify as DTx, the adequacy and rigour of the technical and clinical development cycle, as well as of the authorization procedures, must be fully guaranteed. In addition, it is desirable that availability of these treatments should as far as possible comply with the principle of equal, universal access to care. Ethically, the development and

place in therapy of DTx should create conditions consistent with the concepts of social justice and public health. This means *inter alia* mitigating the risks of a digital divide by creating user-friendly products, making electronic devices (smartphones, tablets, etc.) as widely available as possible, ensuring efficient connectivity, and promoting systematic awareness raising in terms of digital health literacy - both for healthcare professionals and for the population at large.

6. DTx are defined as medical devices, which has clear implications for responsibility in terms of assessment and place in therapy at European and national level. From the European viewpoint, it is not yet known whether DTx can be subject to centralized approval, as is the case for drugs with the European Medicines Agency (EMA); and in some countries, even the role of the national regulatory authorities in the management of DTx needs to be better defined. In the specific case of Italy, the institution responsible is the Ministry of Health. Given the complexity - and considerable variability - of the potential conditions in which DTx are to be used (for example, in combination with drugs), it could be useful to involve other institutions (particularly the Italian Medicines Agency and the National Institute of Health). One proposal could be legal provision for Italy to set up a dedicated commission within the Ministry of Health's General Directorate for Medical Devices and Pharmaceutical Services, thus enabling proper assessment of DTx, negotiation of reimbursement policy, and their inclusion in essential care levels.

7. In Europe, there are already some national models for DTx management. Among these is the German system, active since April 2020, which has already allowed many DTx products to be placed on the market. This system, set up to reconcile healthcare needs (therapeutic value and quality control for treatments) and those of the manufacturers (enabling fast-track authorization under controlled conditions, to limit obsolescence of products and create conditions conducive to possible updates/upgrades), could be considered a valid, useful template for other countries, including Italy.

8. By comparison with other treatments in use (drugs, other medical devices), DTx are characterized by the patient's and/or caregiver's far greater and more active involvement in the care pathway. The reason for this is twofold: the extensive interaction between the digital tool and the

user-patient; and the fact that DTx are used above all for treatment of chronic conditions, associated with lifestyle and dysfunctional behaviours, where the patient's active participation can prove particularly important. DTx afford an opportunity to leverage the patient's experiential knowledge which, from the R&D stage on, complements the scientific knowledge of healthcare professionals and can significantly contribute to optimizing the therapeutic value of these technologies. In addition, implementation of DTx in clinical practice presupposes, as a *sine qua non*, that the patient's engagement must be as discerning and participatory as possible. This must necessarily be ascertained beforehand, by thoroughly assessing the patient's/caregiver's level of confidence with technology.

9. Digital health is a constantly evolving and growing phenomenon. Given the importance of this phenomenon and its delicate nature, Scientific Societies and Patients' and Family Members' Associations should be directly interested and involved in the use, promotion and development of digital health technologies. At the moment, digital health-related initiatives promoted by Scientific Societies and Patient Groups (educational, research and, more generally, awareness raising/knowledge enhancement activities) are, with the exception of a few shining examples, rather limited - particularly so in the case of DTx. There is a clear need for Patients' and Family Members' Associations and groups of healthcare professionals to take on an independent, more active role in leveraging the opportunities offered by digital technologies. These actors can contribute - each within their own field or, ideally, in synergy and in collaboration with other health system stakeholders - to the creation and reinforcement of enabling conditions. This means prioritizing skills, infrastructure and collaborative networks, as well as organized, efficient integration of these technologies into care pathways. Europe, and Italy, can take on a significant role with regard to these therapies. From this perspective, given the extremely rapid evolution of digital health technologies, Scientific Societies and Patients' Associations should work with maximum speed and coordination to develop an active role such as that we envisage here.

10. Currently, the USA are the driving force in the world for development and commercialization of DTx. However, the potential offered by DTx, not only for the scientific and medical world but also for economic development, is equally significant for Europe, as shown by the commit-

ment of some countries to the evolution of this sector. This potential can be realized only if there is an adequate regulatory framework that does not penalize the sector, together with enabling organizational conditions and infrastructure. Such conditions can be achieved only if there is a precise political will and governments are able to lead a fully fledged digitalization process that must be as uniform as possible. A significant boost to this process could be the choice of considering digitalization as one of the main missions of the Recovery Plan proposed by the European Commission, in the wake of the CoViD-19 pandemic. With specific reference to Italy, DTx could prove a significant opportunity in favour of the national health service's efficiency and sustainability, but could also benefit from the excellent environment for growth provided by the country's scientific and industrial setting. Critical issues that could jeopardize the successful development of such opportunities are (at least up to now) limited institutional vision regarding the future of digital health in Italy and, with specific reference to the first DTx products, persistent uncertainty regarding the dissemination of those already approved and used in other countries. However, Italy - like other countries - could receive some positive fallout from the experience of dealing with CoViD-19, which could catalyse a transition towards a broad, structured application of digital health/medicine instruments. This would result in enhanced, and more practical, awareness of the opportunities afforded by DTx.

Lucio Da Ros[1], Giuseppe Recchia[1,2], Gualberto Gussoni[3]

Why a volume on digital therapeutics, and not just for Italy

Defining digital therapeutics

In recent years, terms and expressions like "digital health", "digital medicine", "telemedicine", "virtual patient", "health app", "artificial intelligence for medicine" and "software as a medical device" have become more and more an integral part of scientific terminology and discourse. This is hardly surprising, given the extent to which digitalization is profoundly affecting many sectors of daily life; and the CoViD-19 pandemic, even if we would willingly have done without it, has dramatically amplified and accelerated these transformations. Understandably, against the backdrop of a health emergency, the opportunities offered by digital solutions in the world of health and healthcare (e.g., dematerialized prescriptions and medical reports, remote clinical checks, and digital tracing of contacts - only to mention the most familiar examples) have been receiving a lot of attention from regulatory authorities and from the scientific world.

The terms coined to describe this transformation, when speaking about the application of digital technologies to processes involving health and healthcare ("digital health", "digital healthcare" "e-Health" and others), are used as catch-all labels that often lead to confusion

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and misunderstandings. The digital health dimension does not yet benefit from a standard lexis, and the great variety of disciplines into which the field breaks down are often divided by different languages. The complex, major category of digital health technologies comprises hundreds of thousands of applications and instruments that serve a wide range of purposes - from diagnosis to clinical monitoring, support for medical decision-making, and interventions to address the disease.

The aim of this volume, however, is to focus on one specific category of digital health technologies - so-called **digital therapeutics (DTx)**.

A number of surveys have shown that among healthcare professionals there is a lack of clear knowledge as to what is meant (or what is not meant) by DTx. First and foremost, DTx must not be confused with the host of technologies, systems and platforms that are now part and parcel of everyday life, fulfilling consumer needs related to lifestyle and well-being but, at the same time, serving no direct therapeutic purpose. DTx must also be kept distinct from the various forms of software or hardware used to obtain measurements that could be useful for health purposes. Perhaps even more, the concept of DTx is often, and on the whole inappropriately, associated with applications that are used by the patient and, strictly speaking, fall within the category of so-called patient support programmes (PSP): these include various types of intervention that play a significant role and serve to optimize the patient's ongoing treatment (whether pharmacological or non-pharmacological). In the case of digital PSP, these are mostly apps or web apps serving a number of purposes: to collect the patient's data; enhance his/her communication with the doctor; enable screening for disease, or monitoring of its progression and response to treatment; and, finally, enhance patient compliance. These instruments are often not subject to evaluation by methodologically rigorous clinical trials, while such evaluation is considered a fundamental prerequisite for inclusion in the category of DTx. Quite apart from PSP, in some cases DTx are also confused with so-called digital medicines - i.e., pharmaceuticals with an integrated sensor that is activated once the drug arrives in the digestive tract, triggering a signal to an app housed on a smartphone in order to indicate that the treatment has been taken as prescribed. In other words, these are instruments for monitoring patient compliance, not for implementing the therapy per se: in digital medicines, the active principle is still the molecule and not (as in the case of DTx) the software/algorithm.

So just what do we mean by "DTx"? According to a definition originally proposed by the Digital Medicine Society - Digital Therapeutics Alliance, which is now garnering increasing consensus among the scientific community, the concept of DTx embraces technologies providing therapeutic interventions of proven efficacy, in order to prevent, manage or treat a medical disorder or disease. For illustrative purposes, we can propose an analogy with a drug. Looked at in these terms, every DTx product, which can take such different forms as an app (on a smartphone or tablet) or a video game, comprises an active principle and one or more excipients. Whereas in classical pharmacology the active principle is a chemical or biological molecule, in DTx it is the algorithm that constitutes the therapeutic element responsible for the clinical effect - whether positive (clinical benefit) or negative (undesired effects). With regard to active principle design, we have two main options:

- use an instrument already available in the scientific literature (e.g., a tried and tested cognitive behavioural therapy), In this case, use of DTx becomes an alternative to administration of a known treatment;
- use a brand-new active principle - for instance, by setting up an original combination of different treatment modalities (e.g., cognitive behavioural therapy, motivational interviewing, psychoeducation, etc.), based on the experience of the patient, the caregiver, the medical specialist and the team of developers working on the algorithm. As is the case with traditional drugs, the aim of the excipient is to "give shape" to the active principle and enable the patient to take it, making it as bioavailable - or, in this case, digitally bioavailable - as possible: for this purpose, reward modules and gamification modules introduce an element of patient gratification or of gaming into the dynamics of user interaction with the system. There are also reminders to the patient that they must take the DTx product and complementary therapies, as well as modules to put them in touch with the GP and with other patients following the same therapeutic indication. The excipients can also include the user interface, which plays a fundamental role in making the therapy acceptable, ensuring patient compliance and, as a result, securing the expected therapeutic outcome. It can thus be hypothesized that the same active principle will have a different therapeutic effect according to the digital excipients associated with it in the DTx product, enhancing or decreasing its "availability" to the patient.

How DTx work

But how do DTx work? The main mechanism by which these technologies achieve the therapeutic effect through user interaction is linked **to correction of dysfunctional behaviours**, typical of many chronic diseases - mainly in the neuropsychiatric domain (depression, anxiety, dependencies, insomnia, schizophrenia, autism, attention deficit and hyperactivity disorder in children, etc.), but also for metabolic disorders (obesity, hypertension, diabetes). While drug treatment interacts with the patient's biology, DTx interact with their thoughts and behaviour patterns. In this perspective, another peculiar characteristic of DTx emerges - in other words, the **active and participative involvement of the patient** and/or caregiver, which is of decisive importance for the successful continuation of the treatment pathway. As part of this pathway, DTx can work autonomously and as a standalone modality, or in combination with drugs and other active treatment measures for the target pathology/clinical condition. The editors of this volume are convinced that, if these treatments are indeed able to produce/determine a therapeutic effect, development of DTx should - as is the case for drugs - be based on clinical trials (preferably randomized and controlled), enabling rigorous evaluation of efficacy and safety. On the basis of compliance with technical validation standards (which can be seen as the preclinical phase of the treatment's development), and of evidence generated by clinical trials, DTx should receive the regulatory authorities' authorization as required for clinical use.

Clinical experimentation and the regulatory pathway are two fundamental distinctive features of DTx products, which - unlike the innumerable well-being apps readily downloadable from the Internet - are meant to be prescribed for a therapeutic indication and can possibly be eligible for reimbursement by national health services (generally subject to health technology assessment studies). Fulfilment of these conditions, together with a medical **prescription** (prescription DTx), can be an important qualitative "licence" for DTx, setting them apart and giving them specific recognition within the varied world of digital health. This does not rule out the possibility of digital products for therapeutic purposes, with documented clinical benefits and regulatory validation, being reimbursed through private sector agreements (e.g., through insurance cover) and/or proposed to the patient directly by the manufacturer (as in the case of OTC medicines).

DTx for the health system and the R&D/industrial system

But what is the rationale, in 2021, for a volume dedicated to DTx? First and foremost, DTx are not confined to the future. A number of Western countries have already authorized their use, in some cases also defining the criteria for national health service reimbursement. If the first two decades of the 21st century have been marked by the development and use of the first advanced therapies (gene therapy, stem cell therapy, somatic cell therapy), the 2020s will probably see the clinical availability of many new DTx products that will be proposed in association with - or as an alternative to - tried and tested therapeutic interventions, for the management of many chronic diseases. This is a major therapeutic opportunity, which could help to **significantly improve the outcomes of many diseases** - a factor, in the first instance, which makes them worthy of detailed attention. But the improvement of outcomes will arguably also be associated with an **overall reduction of healthcare and social costs**, favouring the sustainability of health services that, to a greater or lesser extent, make reimbursement available. In this regard, Italy can be a particularly interesting and important case in point, given the universal availability of healthcare under its national health system. These effects are all the more important in that they are essentially related to **chronic diseases**, which account for a clear majority of the resources deployed and the costs borne by health services: in Italy, for example, over 75% of national health funding is used for chronic diseases, and this percentage is bound to grow in the coming years. This is one more reason to give appropriate attention to the dynamics of DTx development and their place in therapy, creating the necessary enabling conditions in organizational, regulatory and financial terms.

But DTx can also be an **opportunity for the manufacturing system** of the countries concerned. In this respect, the United States and the Anglo-Saxon world as a whole are certainly, in the current state of play, the major international players; but the recent arrival of DTx on other national markets (as is the case in Germany and France) can probably be seen as a significant boost for those countries in terms of benefits to research and industry. Italy unfortunately lags behind in terms of digital literacy, and still cannot boast the availability of DTx, but it can offer scientific and technological excellence in the medical and IT-engineering domains. Italy also has a strong tradition of privileging small and medium-sized enter-

prises (SMEs) with a high level of innovation and creativity (which have to date being the driving force of the DTx world, particularly in the early phases of development). These conditions could allow Italy to become a hub for DTx research, development and manufacture, albeit subject to speedy creation of an ecosystem favourable to recognition of innovation in the digital health field. For the development of innovative industrial opportunities, the political decision-makers must send out a clear signal with major implications for patients, healthcare professionals, university research centres and industry, underlining that digital technologies are an integral part of the immediate future in the world of health and medicine. A central element of this process will be the ability to create or enhance the right infrastructure, enabling Italian companies to invest resources in the development of these technologies; this will mean creating value in terms of know-how, jobs and economic return, while also sharing a strategy for reimbursement eligibility and related funding arrangements, so as to guarantee that digital innovations can benefit from a clear and predictable route to the market. It must also not be overlooked that, in terms of clinical research, Italy boasts an organizational track record among the best at international level, and recognized centres of excellence. These are assets that put Italy in a position to play a leading role in DTx clinical research.

This presupposes, however, that the Italian clinical research system will guarantee **speedy regulatory assessment and authorization for trials, with as little red tape is possible**. At the same time, there must be widespread access to **more modern organizational models for clinical trial management**, better suited to the development of digital therapeutics, with appropriate use of technology for data collection and quality control so as to ensure adequate evidence of efficacy and optimal safety monitoring.

In line with these needs, and to promote their fulfilment, the SmithKline Foundation has promoted the development of the *Terapie Digitali per l'Italia - #DTxITA* project, involving a Working Group of about 40 experts from the clinical, academic, regulatory, medico-legal, industrial and health economy fields, together with representatives of Patients' Associations. This group of experts has set as its initial objective the production of this volume, intended first for the Italian public (published in Italian in January 2021) and now updated and with a larger European perspective.

This publication presents a collection of articles on a wide range of

topics that will determine the future of DTx:

- regulatory aspects;
- technical validation and clinical development;
- privacy and cybersecurity;
- possible reimbursement policy in Italy, and the experience of other countries;
- organizational conditions necessary to the success of DTx;
- the position of Scientific Societies and Patients'/Family Members' Associations;
- the patient, digital health and DTx;
- ethics and DTx.

In deciding what specific topics to include this volume, in addition to discussion among the experts in its midst, the Working Group has organized and held meetings with institutional stakeholders, but also with industry (start-ups for digital technology as applied to health; drug and medical device manufacturers; insurance companies, etc.), with Patients' Associations and with the main Scientific Societies nationwide.

The ambition of this project, on a local scale, is to encourage the Italian system, with its long-standing tradition of recognized medical and scientific excellence, not to pass over an opportunity in which the time factor, arguably even more than in other sectors, is all-important. In other words, **what we must do is act, act well, and act quickly**. Further and more generally, and with a vision of potential international interest, this document is intended to provide an up-to-date source of information on the subject, a useful tool for dissemination of knowledge and raising awareness, and stimulus to discussion among institutional, scientific and social stakeholders, including at international level. We trust that the moment has come for current system-related objectives and related investment budgets, as declared by international and national authorities following the CoViD-19 pandemic, to highlight the need for a convergence, never achieved to date, of the health, research and digital innovation dimensions. Such a convergence presupposes thorough knowledge of the issues, and appropriate management strategies. It is our hope that this volume can provide a useful contribution to this end.

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Silvia Stefanelli[4], Federico Sternini[1]

How to manage regulatory aspects for digital therapeutics

1. Regulatory framework

1.1. Definition of a medical device in Directive 93/42/CEE

A medical device was first technically defined within the European legal system in Directive 93/42/CEE, implemented in Italy by Legislative Decree 46/97.

Article 1 letter a) of Directive 93/42/CEE, in the original version, provided the following definition of a medical device:

"any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- *diagnosis, prevention, monitoring, treatment or alleviation of disease;*
- *diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;*
- *investigation, replacement or modification of the anatomy or of a physiological process;*
- *control of conception;*

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means."

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In the light of this definition, the software was therefore not considered as part and parcel of the medical device in its own right, but only insofar as used for the device's correct functioning.

The original version of 1993 was thus intended to regulate the so-called "embedded" software, used to run electromedical devices and to provide an interface for them, while the so-called "stand-alone" software was not described.

1.2. Extension of the definition of a medical device in Directive 2007/47/CEE to include software

In 2007 a new Directive (2007/47/CEE - MDD) was issued, providing a more comprehensive definition of a medical device and establishing that software can be a medical device in its own right.

The implications of this modification clearly emerge in recital 6 of the Directive, which states:

"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, is a medical device. Software for general purposes when used in a healthcare setting is not a medical device."

Recital 20 then states:

"Taking account of the growing importance of software in the field of medical devices, be it as stand alone or as software incorporated in a device, validation of software in accordance with the state of the art should be an essential requirement."

The definition of a medical device is therefore reformulated as follows:

"any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- *diagnosis, prevention, monitoring, treatment or alleviation of disease;*
- *diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;*
- *investigation, replacement or modification of the anatomy or of a physiological process;*
- *control of conception;*

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means."

Starting from 2007, legislation has thus established that software can be considered a medical device itself, wheter it is incorporated in the device (embedded) or works in its own right (stand-alone).

Subsequently, the international IMDRF/SaMD WG/N10FINAL:2013 guidelines introduced the following definition of software as a stand-alone medical device (also called Software as a Medical Device - SaMD):

"The term "Software as a Medical Device" (SaMD) is defined as software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device."

1.3. Regulation (EU) 2017/745 on medical devices

In 2017 the new Regulation (EU) 2017/745 on medical devices was approved. Known as the MDR (Medical Device Regulation), this will also be referred to below simply as the Regulation. When it was published in the official Gazette of the European Union on 5 May 2017, the intention was for it to supersede the current Directive and enter into force on 26 May 2020. However, in April 2020, because of the CoViD-19 pandemic, the European Parliament postponed the entry into force of the new Regulation and extended the period of validity of the current Directive by one year, thus establishing the new date of the Regulation's formal application as 26 May 2021. It should be noted that the Regulation, unlike the Directive, is a full-fledged legislative act, binding in all its parts, which does not need to be transposed into national legislation and thus obliges the member states to comply with it in its entirety.

The new MDR extends the definition of a medical device, including prediction and prognosis among the purposes taken into account, and thus potentially also including software for risk index calculation.

Regarding application of the new rules to software in particular, it is important to point out that Article 2, point 28 of the MDR defines placing on the market as "the first making available of a device, other than an investigational device, on the Union market ".

Article 5 then states that: *"A device may be placed on the market or put into service only if it complies with this Regulation when supplied and properly installed, maintained and used in accordance with its intended purpose."*

Recital 19, with the aim of better defining when software is a medical device, states: *"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."* So-called wellness apps, meaning those for simple lifestyle tracking, are thus excluded from the definition of a medical device because they are not for "diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of diseases", while those for tracking and collecting everyday lifestyle data for purposes of primary or secondary prevention do fall within the medical device category.

Regarding the manufacturer's responsibilities, defined in Article 10 of the Regulation, two of the most important are:

- the need to adopt a system for risk management throughout the medical device's life cycle, from design to disposal, with a requirement for new, more detailed assessment of post-certification data;
- the obligation to assess the clinical benefits of the product.

Annex 1 of the Regulation includes a list of essential requirements that must be taken into account by the manufacturer for all devices, irrespective of their risk class. To demonstrate conformity with applicable requirements, the manufacturer must adopt different strategies (analyses, tests or procedures): typically, compliance with international/harmonized standards, where available, is considered the most appropriate strategy.

In the case of digital therapeutics, the most appropriate international standards are ISO 13485 and EN ISO 14971 for general requirements, followed by IEC 62304 and IEC 62366 with specific reference to the product's life cycle and usability.

1.4. Risk classes and medical device software

To identify the medical device's risk class, its intended use and the related intrinsic risk must be analysed. Identification of the device's risk class makes it possible to define which strategies and procedures are needed to demonstrate its conformity with the Directive or Regulation.

These procedures are designed with a view to resource allocation by the notified bodies and manufacturers, on the principle that high-risk devices require more rigorous testing, while lower-risk devices can be subjected to less costly verification procedures without jeopardizing the patient's safety.

Medical devices are divided into four risk classes, with the associated degree of risk numbered in ascending order as shown below:

- Class I: less critical devices, such as most non-active and non-invasive devices.

This class comprises three subclasses:

Class Is: devices delivered in a sterile state

Class Im: measuring devices

Class Ir: reusable devices (a new subclass, introduced by the MDR);

- Class IIa: medium-risk devices, such as some non-active devices (both invasive and non-invasive) and active devices that interact with the body in a non-hazardous manner;
- Class IIb: medium-/high-risk devices, such as some non-active devices (especially if invasive) and active devices that interact with the body in a hazardous manner;
- Class III: high-risk devices, such as many implants, those containing drugs or animal derivatives, and some devices that interact with vital organ functions.

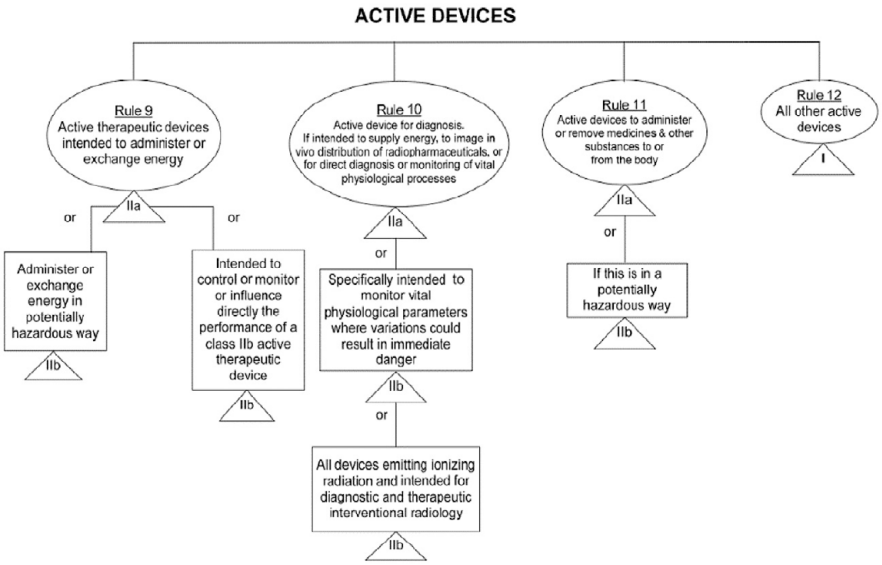
Regarding software, both the Directive and the Regulation specify that the classification rules for active devices must be applied. In addition, the Regulation expressly sets out specific rules for software, thus filling a regulatory gap not addressed by the Directive.

The classification rules provided in both the Directive and the Regulation are summarized below, bearing in mind the intention that the former is now superseded by the latter. This reclassification will have important implications, since it will mean that many software products currently included by the Directive in class I will need to be moved into a higher risk class when re-classification will be necessary.

The Directive sets out the rules for classification in Annex IX, where software is specifically covered by rules 9, 10, 11 and 12. These rules were extensively described and commented on by MEDDEV 2.1/6 of July 2016 and MEDDEV 2. 4/1 Rev. 9 of June 2010 (from which the figure below is reproduced).

The new classification rules set out in Regulation (EU) 2017/745 can

Figure 1 - Rules applicable until the coming into force of the new MDR for definition of an active device's risk class



MEDDEV 2. 4/1 Rev. 9 June 2010

be found in Annex VIII, rule 11:

"Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class IIa, except if such decisions have an impact that may cause:

- *death or an irreversible deterioration of a person's state of health, in which case it is in class III; or*
- *a serious deterioration of a person's state of health or a surgical intervention, in which case it is classified as class IIb.*

Software intended to monitor physiological processes is classified as class IIa, except if it is intended for monitoring of vital physiological parameters, where the nature of variations of those parameters is such that it could result in immediate danger to the patient, in which case it is classified as class IIb.

All other software is classified as class I."

During the current period of transition towards application of the new Regulation, there is a clear need to look in greater detail at the different classifications and how they are related to each other, since they all

have an impact with a view to handling of post-transition activities. In this regard, the European Commission has recently published a steering document, in the form of specific guidelines on regulatory aspects of software under the MDR and IVDR (MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 - MDR and Regulation (EU) 2017/746 - IVDR): this is seen as a source of guidance in determining whether software falls within the definition of a medical device, as well as in subsequent identification of the corresponding risk class.

Th e CE marking class, defined on the basis of the certification rules set out in the Regulation, depends on the intended use of the software (when this is consistent with the manufacturer's recommendations in conditions of normal use). An important implication of this, for the procedure to be followed in obtaining CE marking and placing the software on the market, is the mandatory involvement of a notified body for devices in risk class IIa or higher (meaning, under the new Regulation, practically almost every software fulfilling the definition of a medical device).

The risk class must therefore be determined by analysing the intended use of the software, which can be described in terms of:

- target patient population
- intended users (professional, non-professional, patients)
- clinical performance
- expected clinical benefit.

Briefly stated, risk classes can be broken down as follows for a standalone medical device software *(Table 1)*.

Table 1 - Risk class and CE marking for software as a medical device according to the MDR, with examples

Class	Description in MDR (rule 11)	Examples
III	Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes; only insofar as such decisions have an impact that may cause "death or an irreversible deterioration of a person's state of health"	Software suggesting a diagnosis of a heart attack in progress, based on ECG, in an emergency situation Software for recognition of shockable heart rhythm Software suggesting treatment options from image analysis in acute stroke patients

IIb	Software intended to provide information which is used to take decisions with diagnostic or therapeutic purposes; only insofar as such decisions have an impact that may cause "a serious deterioration of a person's state of health or a surgical intervention" Software intended to monitor "vital physiological parameters, where the nature of variations of those parameters is such that it could result in immediate danger to the patient"	Software for calculating dosage of a contrast medium Software for augmented reality in surgical planning Software for monitoring respiration in unconscious patients
IIa	Software intended to provide information which is used to take decisions with diagnostic or therapeutic purposes; only insofar as such decisions do not have an impact that may cause "death or an irreversible deterioration of a person's state of health" or "a serious deterioration of a person's state of health or a surgical intervention" Software intended to monitor physiological processes, other than "vital physiological parameters, where the nature of variations of those parameters is such that it could result in immediate danger to the patient"	Software for recognition of sleep apnea Software to evaluate the depth and extension of bed sores Software for sleep tracking Software for monitoring of diuresis
I	All others	See example in MDCG 2019-11 Guidelines *

* MDSW app intended to support conception by calculating the user's fertility status based on a validated statistical algorithm. The user inputs health data including basal body temperature (BBT) and menstruation days to track and predict ovulation. The fertility status of the current day is reflected by one of three indicator lights: red (fertile), green (infertile) or yellow (learning phase/cycle fluctuation). This MDSW app should be classified as class I, as per Rule 11c.

1.5. Medical device software classification: some considerations and a proposal

The MDCG 2019/11 'Guidance on Qualification and Classification of Software' document, mentioned above, specifies the requirement that the software be used for the benefit of a single individual; this means that it explicitly excludes software used for epidemiological research, or in relation to generic guidelines or clinical protocols that are not patient-specific. On

the basis of the MDCG 2019/11 document, it becomes clear that software to be used in managing a single individual's personal diagnostic procedures and course of treatment is to be considered a "medical device software", or MDSW. The brief mention of software for planning of treatment pathways, in Decision step 4 (paragraph 3.3), seems to be the only reference in MDCG 2019/11 to the fact that software can perform a therapeutic action. Specifically, the document provides the following comment on rule 11 of the MDR, which is already sufficiently clear and explicit:

"The text of Rule 11 can be divided into what are essentially three sub-rules that are applied depending on the intended use/purpose of the MDSW:

11a: (3 first paragraphs of Rule 11) intended to provide information which is used to take decisions with diagnostic or therapeutic purposes;

11b: (Paragraph 4 of Rule 11) intended to monitor physiological processes or parameters;

11c: (Paragraph 5 of Rule 11) all other uses."

Judging by the few specific references in MDGC 2019/11, ***the authors seem not to have given detailed consideration to the possibility that software may exert a therapeutic action***, while the following possible functions are identified:

- data analysis so as to provide a human being, or another software, with information that can be used to take clinical decisions
- monitoring.

MDGC 2019/11 even states the following (paragraph 4.2.1):

"The wording '***intended to provide information*** which is used to take decisions with diagnosis or therapeutic purposes' describes, in very general terms, the 'mode of action' ***which is characteristic of all MDSW***."

It thus seems that the legislators are not specifically taking into account the possibility that therapeutic effect is achieved by the software itself, since the feature they identify as common to all MDSW is the function of providing information (processed from input to output).

In addition, it should be noted that not even the many examples provided by the guidelines, with respect to specific types of software and their classification, include any mention of the possibility that they might be used for therapy. The only exception is an example of "Cognitive therapy MDSW that includes a diagnostic function": this is classified in class III if the diagnostic function is on a closed loop basis, but in class IIa if it provides information to the doctor. Not even in this case, however, is the therapeutic function explicitly considered as a criterion for classification. An-

other example mentioned is the following: *"Diagnostic MDSW intended for scoring depression based on inputted data on a patient's symptoms (e.g. mood, anxiety) should be classified as* ***class IIb under Rule 11(a)***".

As a result of this, software intended to provide therapy, such as rehabilitative or cognitive-behavioural therapy, **could be erroneously placed under the heading "all other uses" and considered as class I**.

This interpretation of the classification rules would lead to the risk of classifying **all digital therapeutics (DTx) MDSW** in class I. We consider that this interpretation is **a rapid but dangerous short cut**, because it would lead to an erroneous classification in a low risk class for a miscellaneous group of MDSW, including some whose scheduled use has a major impact on the patient's health.

On the other hand, it should be noted that where a drug in its presentation incorporates a medical device (and, thus, also a SW), whether or not as an integral part, it is defined as a Drug-Device Combination (DDC).

If the drug is an integral part of a device, the relevant part of the MDR is the second sub-paragraph of Articles 1(8) and 1(9):

"1. Devices that when placed on the market or put into service incorporate, as an integral part, a substance that, if used separately, would be considered as a medicinal product, provided that the action of the substance is principal (Article 1(8) MDR). 2. Devices intended to administer a medicinal product, where they form a single integral product intended exclusively for use in the given combination and which is not reusable (Article 1(9) MDR). Typically, these devices have measuring, metering or delivery functions". The reference document on the subject of drug-device combinations is currently in draft form[**].

A possible classification of stand-alone DTx can be found in the following table *(Table 2)* included in MDCG 2019-11, point 11, Annex III. By combining indications of the IMDRF document "Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations" with provisions of Rule 11 - MDR Annex VIII, this table provides operators placing MDSW on the EU market with some useful indicative guidance on the risk class applicable to their products. It is also relevant to point out that this table is actually the only point in the entire document where the word "treat" is explicitly mentioned.

The table shows that **therapeutic software is placed in class III, IIb or IIa, according to how critical a condition it is intended to be treated.**

[**]29 May 2019 EMA/CHMP/QWP/BWP/259165/2019. Committee for Medicinal Products for Human Use (CHMP). Guideline on the quality requirements for drug-device combinations.

Table 2 - Classification of MDSW according to MDCG 2019-11

		Significance of Information provided by the MDSW to a healthcare situation related to diagnosis/therapy		
State of Healthcare situation or patient condition		**High** Treat or diagnose *~ IMDRF 5.1.1*	**Medium** Drives clinical management *~ IMDRF 5.1.2*	**Low** Informs clinical management *(everything else)*
	Critical situation or patient condition *~IMDRF 5.2.1*	**Class III** *Category IV.I*	**Class IIb** *Category III.I*	**Class IIa** *Category II.I*
	Serious situation or patient condition *~IMDRF 5.2.2*	**Class IIb** *Category III.II*	**Class IIa** *Category II.II*	**Class IIa** *Category I.II*
	Non-serious situation or patient condition *(everything else)*	**Class IIa** *Category II.III*	**Class IIa** *Category I.III*	**Class IIa** *Category I.I*

Class I is not included in the table and, even for the least critical level considered (i.e., for "non-serious" conditions), class IIa is proposed.

This means that, bringing together the different indications stated in the IMDRF framework document's conversion table and in the EU classification rules as set out in the MDR, the lowest class for any therapeutic software would be class IIa.

The regulatory implications of this are very important, indeed vital. Specifically, only in class I there is provision for the device to receive the CE mark and be placed on the market on the sole basis of a manufacturer's self-declaration. In all other cases, the Directive and the Regulation specify that, for classes IIa and higher, a notified body must be involved in the certification process.

We therefore find it of great interest that the authors of the Guidelines provide specific examples for DTx, when applied to software with an intended therapeutic function. In addition, it is appropriate that the Guidelines and/or the illustrative examples should provide further comments on the correlation between the severity of the condition to be treated with

therapeutic software and the corresponding risk class, incorporating the examples already present in Annex IV.

The classification of DTx into classes IIa, IIb and III, according to the severity of the condition to be treated and the corresponding risk, allows a good degree of consistency between the regulatory requirements already applicable to diagnostic and therapeutic software. Indeed, rule 11 of the MDR establishes medium to high risk classes for monitoring and diagnostic software: the more critical the monitoring or diagnosis, the higher the class.

The model in *Table 3* (see below) shows examples of classification for MDSW with a therapeutic function, in order to focus more closely on the peculiar features of DTx.

Table 3 - Proposed classification of MDSW with a therapeutic function, showing examples

Class	Rule 11	Proposed interpretation of rule 11 for DTx	Examples
III	Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes; only insofar as such decisions have an impact that may cause "death or an irreversible deterioration of a person's state of health"	Intended for therapeutic use, where this is necessary to protect an individual patient from death, long-term disability or other severe deteriorations in health	Software for therapy of schizophrenia
IIb	Intended to provide information which is used to take decisions with diagnostic or therapeutic purposes; only insofar as such decisions have an impact that may cause "a serious deterioration of a person's state of health or a surgical intervention"	Intended for therapeutic use, where this is necessary to mitigate irreversible and/or long-term health consequences for an individual patient or for public health	Behavioural therapy software, used to complement/replace pharmacological therapy for drug/alcohol dependence Behavioural therapy software, used to manage eating disorders such as anorexia and bulimia

IIb	Intended to provide information which is used to take decisions with diagnostic or therapeutic purposes; only insofar as such decisions have an impact that may cause "a serious deterioration of a person's state of health or a surgical intervention"	Intended for therapeutic use, where this is necessary to mitigate irreversible and/or long-term health consequences for an individual patient or for public health	Behavioural therapy software, used to complement/replace pharmacological therapy for drug/alcohol dependence Behavioural therapy software, used to manage eating disorders such as anorexia and bulimia
IIa	Intended to provide information which is used to take decisions with diagnostic or therapeutic purposes; only insofar as such decisions do not have an impact that may cause "death or an irreversible deterioration of a person's state of health" or "a serious deterioration of a person's state of health or a surgical intervention"	Intended for therapeutic use, where this is important but not critical with a view to mitigating irreversible long-term health consequences for an individual patient or for public health	Behavioural therapy software, used to slow down cognitive decline typical of senile dementia Behavioural therapy software, used to enhance learning capacity in persons with Down syndrome Virtual reality software used as a complement to physiotherapy, creating an avatar of the patient to simulate movement of an amputated limb
I	All others		See example in MDCG 2019-11 Guidelines ***

*** MDSW app intended to support conception by calculating the user's fertility status based on a validated statistical algorithm. The user inputs health data including basal body temperature (BBT) and menstruation days to track and predict ovulation. The fertility status of the current day is reflected by one of three indicator lights: red (fertile), green (infertile) or yellow (learning phase/cycle fluctuation). This MDSW app should be classified as class I, as per Rule 11c.

1.6. Regulatory obligations

Like all medical devices, DTx must respect the essential requirements set out in the current Directive, carried over into the new Regulation but with a number of important updates, above all regarding the obligations in relation to demonstration of clinical benefit.

The manufacturer's obligations can be summed up in the three keywords "**safety**", "**benefit**" and "**quality**". Compliance with these obligations is based on the application of international standards.

- **Safety**

For demonstration of **safety**, the reference standard to be consulted by DTx developers is IEC 62304: the version currently in force is dated 2006, but this is at present undergoing widespread and significant revision. It defines methods to design, develop and test software, as well as to manage its entire life cycle, including any updates.

Application of this standard must necessarily go hand in hand with that of ISO 14971, on risk management, dealing in particular with design, testing and updating activities. Application of this standard makes it possible to demonstrate that the software is free of any structural defects constituting a possible risk for the patient, or interfering with its correct functioning in terms of technical performance.

The software's safety class, defined in compliance with the technical standards set out in IEC 62304, depends on the severity of the damage caused by any breakdown of the software. This class determines the required level of stringency with which the manufacturer must carry out design and functional testing *(Table 4)*.

Table 4 - Software safety classes defined in accordance with the IEC 62304 technical standard

Class	Description in MDR (rule 11)	Examples
C	The software can contribute to a situation of danger that generates unacceptable risks after taking into account risk control measures extraneous to the software system, resulting in possible damage of a "serious" nature.	Software for recognition of shockable heart rhythm Software for cognitive-behavioural therapy in a disease leading to alterations in the state of consciousness (epilepsy, narcolepsy) or in the perception of reality (manias, schizophrenia)

B	The software can contribute to a situation of danger that generates unacceptable risks after taking into account risk control measures extraneous to the software system, resulting in possible damage of a "non-serious" nature.	Software for monitoring diuresis (a malfunction of the software can mean failure to diagnose an acute renal insufficiency)
A	The software cannot contribute to a situation of danger. The software can contribute to a situation of danger that does not involve unacceptable risks after taking into account risk control measures extraneous to the software system.	Software for cognitive-behavioural therapy in a disease not leading to alterations in the state of consciousness or in the perception of reality Software suggesting a diagnosis of a heart attack in progress, based on ECG, in an emergency situation; in the event of a scheduled procedural control excluding the possibility of taking a therapeutic decision based solely on this information, but requiring assessment of other, clinically more relevant data such as analysis of cardiac enzymes (WHO Guidelines)

We consider it important to point out that, with a view to the essential criterion of fulfilling requirement 17 of the MDR, the manufacturer must apply management principles to the software's entire life cycle: these principles are clearly set out in the IEC 62304 standard, the harmonized version of which is EN 62304. Application of harmonized standards makes it possible to presume compliance with essential requirements: this standard thus becomes a technical instrument of major importance for purposes of achieving compliance with the MDR.

It should be emphasized that classification in risk classes from I to III, in accordance with the MDR, and classification in risk classes from A to C, in accordance with IEC 62304, are not formally interrelated. Classification must be established by the manufacturer on a case-by-case basis.

- **Benefit**

For demonstration of **benefit**, the reference standard to be consulted by DTx developers is ISO 14155, on good clinical practices for investigation of medical devices. Application of this standard involves demonstrating that, in the target population, the software can achieve clinical benefit significantly outweighing the potential risk involved in its use. In practice,

this means moving from indicators of technical performance and safety to indicators of clinical benefit and safety.

Typically, the risk/benefit ratio is investigated in small samples, obviously while ensuring that numbers are appropriate for good statistical evaluation. These studies should include endpoints both for safety (measurement of which often includes any technical malfunction) and for clinical efficacy. It is just as important to note that clinical benefit can be expressed both in terms of health or quality of life in a single patient and also in terms of positive impact on the management of the treatment pathway, as judged by applying Health Technology Assessment (HTA) indicators.

In this perspective, it is worth reiterating the definition of "clinical benefit" in Article 2.53 of the MDR: *"the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health."*

In addition, Meddev 2.7/1 rev 4, though partly superseded by MDCG 2020-1 Guidance on Clinical Evaluation (MDR)/Performance Evaluation (IVDR) of Medical Device Software, offers guidance that is still relevant with regard to identification and evaluation of "benefits for the patient" (paragraph A.72.b):

Evaluation of the device's benefits to the patient

Positive impacts of a device on the health of an individual should be meaningful (relevant for the patient) and measurable. The nature, extent, probability and duration of benefits should be considered. Benefits may include:

- *positive impact on clinical outcome (such as reduced probability of adverse outcomes, e.g. mortality, morbidity; or improvement of impaired body function);*
- *the patient's quality of life (significant improvements, including by simplifying care or improving the clinical management of patients, improving body functions, providing relief from symptoms);*
- *outcomes related to diagnosis (such as allowing a correct diagnosis to be made, provide earlier diagnosis of diseases or specifics of diseases, or identify patients more likely to respond to a given therapy);*
- *positive impact from diagnostic devices on clinical outcomes, or*
- *public health impact (such as to the ability of a diagnostic medical device to identify a specific disease and therefore prevent its spread, to identify phases, stages, location, severity or variants of disease, predict future disease onset).*

Also of great interest is the following comment from the more up-to-date MDCG 2020-1 Guidance on Clinical Evaluation (MDR)/Perfor-

mance Evaluation (IVDR) of Medical Device Software, covering as it does the question of benefits not measurable through specific clinical outcomes of a patient:

"Specifically, for MDSW not claiming CLINICAL BENEFITS that can be specified through measurable, patient-relevant clinical outcome(s), clinically relevant outputs are achieved through demonstrated predictable and reliable use and USABILITY (please refer to section 4.2 of this document)."

- **Quality**

To demonstrate **consistent quality over a period of time**, the reference standard for DTx developers is ISO 13485, ***Medical devices - Quality management systems - Requirements for regulatory purposes***. A harmonized and internationally recognized standard, this document sets out the requirements for a quality management system specifically relevant to the medical devices industry. While an ISO 13485:2016 certification is not mandatory, it not only helps the organizations involved in every stage of a medical device's life cycle to demonstrate its compliance, but also provides all stakeholders with appropriate communication strategies.

In this respect, a central consideration for DTx is the need to guarantee management of the software's life cycle, including any corrective modifications (bugfixes, perfective maintenance) and/or incremental improvements, as well as for user notification regarding any modification and its effect on the software.

For the technical considerations identified in the previous paragraph, it is again appropriate to consult the IEC 62304 standard, in the draft version of which the manufacturer of a medical device must:

"ensure that the released health software can be reliably delivered to the point of use, without corruption or unauthorized modification."

In addition, IEC 62304 also requires that the manufacturer adopt a procedure for control of any subsequent version. For DTx devices, versioning policy should be based on the impact that a version will have on standard requirements. For example, the entire DTx system could comprise various modules, with separate SW versions for:

- the algorithm;
- the professional user interface; with different versions related to different operating environments (for example, access via Android App from a smart device);
- the patient interface; again with different versions related to different

operating environments (for example, access via Android apps from a smart device).

We propose structured control over SW versions of the released software, consistent with standard practice for software design, as in major.minor.build semantic versioning:

- the "major" number increases in relation to significant advances in function, like modification of the framework that could alter the risk-benefit profile;
- the "minor" number increases in relation to additions, corrections or improvements affecting only minor functions;
- the "build" number increases in relation to correction of bugs.

In addition, version control can include the possibility of a "release candidate" version; in the event of the version undergoing a major or minor modification, the "candidate version" is the SW version available only to selected partners for the pilot assessment and/or only in a controlled environment, separate from the commercial environment.

The Food and Drug Administration (FDA) proposes a risk-based approach to modification of software, pointing out the need to ensure that the testing and validation stages benefit from availability of greater resources where a new version involves:

- introduction of a new risk, or modification of an existing risk, with potential to create significant damage;
- modification to risk controls, to prevent significant damage;
- modification significantly affecting the device's clinical function or performance specifications.

Where applied to DTx with artificial intelligence modules, the above approach would require special attention in cases where any update:

- significantly affects the device's performance or safety and efficacy;
- impacts the scheduled use of the device, for example by increasing the target population;
- introduces important technical modifications affecting performance characteristics.

In addition, the FDA encourages developers to assess the impact of the change on three characteristics of the SaMD:

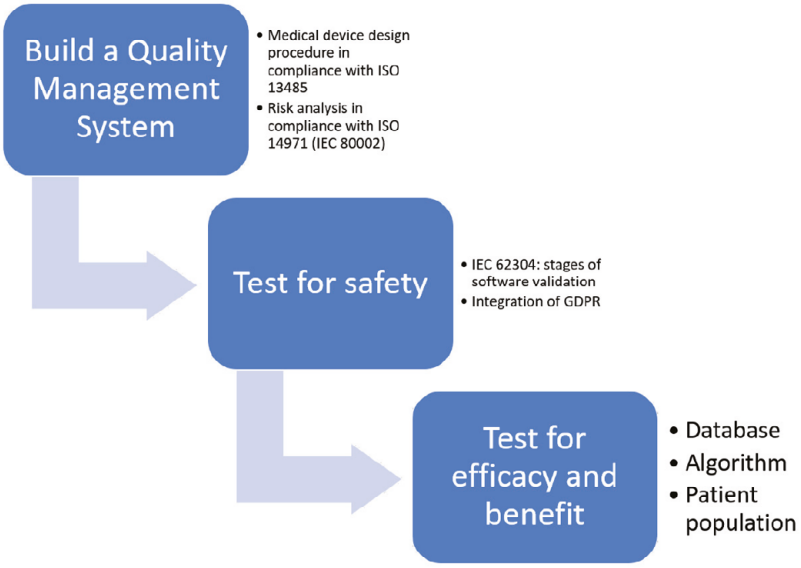
- performance (clinical and analytical);
- inputs used by the algorithm, and their association with clinical output;
- scheduled use, as described by the DTx's impact on the disease condition.

1.7. Our proposal for an approach to regulatory procedures: how to develop software consistent with the definition of DTx

The flow diagram in *Figure 2* illustrates a suggested approach to medical software design, with a view to ensuring that design activities fulfil regulatory requirements from the very outset. The proposal is therefore to set up a quality system based on ISO 13485, in order to guarantee correct management of medical device designed, including compliance in terms of risk management. After this, it is recommended that a software life-cycle management system be set up according to IEC 62304, thus guaranteeing compliance in terms of the software's technical validation and correct management of development problems. In addition, when applying IEC 62304 to software design, it is also recommended that the principles of data protection enshrined in GDPR should be fully incorporated where applicable. Finally, when the development phase and the technical validation of the device's safety have been completed, it is recommended that the device's technical efficacy be tested with simulated patients.

The first step in setting up medical device software design should therefore be to define the project inputs, as required by ISO 13485 and described

Figure 2 - Proposed development sequence for DTx software



elsewhere in this volume (see "Technical validation of digital therapeutics"). The result of the design phase described so far should be a list of the software's functions for each user profile. Project requirements thus identified should include the methods used to mitigate any risk for the patient.

It is also suggested that the patients themselves should be involved, starting from the input definition phase, using participatory project planning techniques both to define user needs and to consolidate user experience.

In defining functions, it will be necessary to clearly identify the expected clinical benefit: for correct planning of clinical trials in terms of measurable endpoints, it will then be important to define appropriate metrics for the measurement of the expected benefits, in compliance with MDCG 2020-1 Guidance on Clinical Evaluation (MDR)/Performance Evaluation (IVDR) of Medical Device Software.

Full definition of project requirements will be followed first by the development phase, and then by technical testing. For this phase, functional testing of the device should follow a plan based on the list of input requirements, thus ensuring that risk minimization measures can also be included.

Once validation testing of software function has been completed, above all in terms of patient safety, the device's usability should be assessed by an iterative approach in compliance with IEC 62366: this will ensure testing of the interface for an appropriate usability profile, in a simulated environment but with the participation of real users.

Where the device is also intended for direct use by patients, they should be involved in these tests.

Only after technical and usability testing in a simulated environment is it advisable to move on to assessment of the device's efficacy. Before clinical investigation, it is advisable that technical validation should be completed with simulation of real clinical use, involving patients expressly identified for this purpose and representative of the device's probable user population (Ravizza A. et al. Method for preclinical validation of software as a medical device 2020. DOI: 10.5220/0009155406480655).

To create the profiles of these "simulated patients", it is a good idea to use available data (subject, of course, to prior consent) or data from the literature. These data should be used to identify the characteristics that can best describe the patients in relation to the device, including parameters such as:

- reaction time after appearance of a visual stimulus, in the case of a device for visual rehabilitation;

- responses to self-assessment questionnaires, in the case of devices managing side effects of chemotherapy;
- daily calorie intake, in the case of a device for treatment of pre-diabetes.

The statistical measure recommended for these data is the mode, making it possible to create different patient profiles as representative as possible of a real clinical situation. The rationale for preferring the mode to the mean is that the latter, while providing a basis for statistically significant models, could lead to identification of a simulated patient who would not be representative of a real clinical condition or of real interaction with the device. For example, if respondents to a questionnaire are asked to indicate the level of pain on a scale from 1 to 5, and three quarters of them indicate 1 while the remaining quarter indicate 5, the result of applying the statistical mean would be a value of 2 for pain - not actually representative of any single patient. For this reason, it is suggested that the device be tested with a simulated patient giving the answer 1, since this will at least prove representative for three quarters of the patient population.

What is known

- The applicable regulations
- The applicable technical standards
- The possibility of bringing together the concepts of safeguarding health, data protection and cybersecurity
- Critical issues and ambiguities in current regulations.

What is uncertain

- The approach of notified bodies when applying standards to DTx, particularly where artificial intelligence is involved
- In some countries, the role played in regulatory procedures by the health authorities (e.g., in Italy: Ministry of Health and related technical bodies on the one hand, Italian Medicines Agency on the other).

What we recommend

- Clear indications and examples for classification in classes I, IIa, IIb and III
- Guidelines for control of software versions, defining policies for classifying major and minor changes of version.

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Technical validation of digital therapeutics

1. Foreword

As is the case with other medical devices, Digital Therapeutics (DTx) too must comply with the essential requirements set out in European standards. These requirements were defined in the current Directive and reconfirmed, albeit with important new features related to the demonstration of clinical benefit, by the new Regulation 2017/745/CE. The requirements as they now stand can be summed up in three keywords: **safety**, **efficacy** and **quality**. Manufacturers can demonstrate that they have fulfilled the obligations set out in the essential requirements by applying international standards.

In this text, the authors focus on the process of development and technical validation of DTx as defined in the ISO 13485 and IEC 62304 standards, up to and including the stage immediately before clinical validation.

2. Fundamentals of technical validation for DTx

Design and technical validation of DTx must be carried out according to the regulatory requirements for medical devices. This means that design must comply with quality system requirements as set out in ISO 13485, and with software life-cycle management requirements as detailed in IEC 62304.

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The above-mentioned standards determine the need for consistent and structured definition of clinical needs, and of technical, regulatory and privacy-related constraints, all of which play a decisive role in defining the development planning process for the minimum viable product (MVP) and the final product. The MVP will be used during the various phases of technical validation in order to ensure safety, and will then be brought forward to testing in the field, first for usability and then for the various clinical use pilot phases.

In order for the product to be correctly certified as a medical device, design input requirements must include risk minimization measures consistent with a thorough prior analysis of technical and clinical risk, carried out by the manufacturer in compliance with ISO 14971. A non-exhaustive list of the most useful techniques for DTx risk analysis includes:

- FMEA - failure mode and effects analysis (specifically, inputs defined as per ISO 14971 and IEC/TR 80002-1);
- FTA - fault tree analysis.

These techniques are complementary, with FMEA following an inductive approach while FTA is based on deductive reasoning. On the one hand, FMEA uses initial observation of particulars and identification of failures that have occurred to single components in order to identify system failures; by contrast, FTA begins with general, overall analysis of the type of undesired event (or failure) and uses this as the basis to identify failures of individual components.

Consistent with ISO 13485, development can thus be broken down into a sequence of four main points: definition of intended use, definition of main features, identification of risks, and identification of regulatory constraints. For DTx, each of these four points can be broken down into the subheadings shown below:

1. Identification of intended use, in relation to the parameters listed below
   a. therapeutic/diagnostic area
   b. task/purpose
   c. patient population
   d. user (patient, caregiver, healthcare professional)
   e. claimed benefits, including measurable clinical indicators.
2. Requirements, in terms of function, performance, usability and safety, according to the intended use
   a. available functions and their expected results (e.g., delivery of therapy at specific times of day; visualization of state of therapy)

b. technical performance that has to be guaranteed in order to achieve correct use of the device (e.g., how many users at the same time, interaction time)
c. intended forms of user-device interaction (e.g., visualize, select from a list, interact with treatment coordinator, voice command)
d. conditions/situations requiring notification to user (e.g., time almost up)
e. which solutions need to be guaranteed for data protection.

3. Identification of main risks
a. as a result of performance not achieving required levels of accuracy (e.g., failure to achieve appropriate accuracy in measuring a specific parameter, or to recognize a clinically dangerous situation)
b. as a result of software malfunction (e.g., loss of data, or failure to post an "alarm" message)
c. as a result of error in software use (e.g., misinterpretation of an "error" or "alarm" message)
d. other specific risks of the software (e.g., failure to synchronize).

Risks must be identified at this stage, since the software will have to be designed with a view to minimizing both the likelihood of their occurrence and their impact on the patient's safety. During testing, it will also be necessary to demonstrate that appropriate measures have been taken at the design stage, in order to minimize risk, in the light of regulatory constraints.

4. Identification of major regulatory constraints
a. class of CE mark
b. software risk class as per IEC 62304
c. where applicable: data protection, in compliance with GDPR
d. where applicable: cybersecurity, in compliance with Regulation 2019/881.

3. Minimum required details of DTx to activate the clinical validation phase

3.1. Initial development phase

Initial development techniques for software have not been particularly impacted by regulatory constraints, even if thorough reporting of the various iterations involved can prove helpful for the subsequent validation phase.

DTx manufacturers must nevertheless, even at this stage, determine a number of important indicators for subsequent validation. A non-exhaus-

tive list of these indicators includes the following:

- protective measures against the risk of hacking
- measures for anonymization and pseudonymization of data
- management of the reference hardware (off-the-shelf or dedicated)
- management of any software of unknown provenance (SOUP)
- management of GDPR compliance techniques.

According to IEC 62304, SOUP means software items that are already developed and are generally available, and that have not been developed for the purpose of being incorporated into the medical device (also known as "off-the-shelf" software), or software items previously developed for which adequate records of the development processes are not available.

Some examples of this are the following:

- device drivers
- operating systems (including app operating systems, such as Android and iOS)
- runtimes, including all libraries and programmes that enable running of the software but are not part of the operating system (e.g., virtual machines, libraries for memory allocation).

3.2. Technical verification

The purpose of the technical verification phase is to demonstrate that the software fulfils technical and performance requirements, as specified in the project documentation. The verification phase must be completed in accordance with IEC 62304, the requirements of which become increasingly stringent for higher safety classes.

IEC 62304 subdivides software into three safety classes, according to the severity of damage caused in the event of its failure. Class A comprises software that cannot cause damage; software in class B can cause "non-serious" damage; class C is for software that can lead to "serious" damage.[*] This

[*] The following definition is proposed:
A serious deterioration in state of health can include (non-exhaustive list from MEDDEV 2.12_1), in accordance with ISO 14155:2020:
a) life-threatening illness,
b) permanent impairment of a body function or permanent damage to a body structure,
c) a condition necessitating medical or surgical intervention to prevent a) or b).
- Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalisation.

d) any indirect harm (see definition under section 4.11) as a consequence of an incorrect diagnostic or IVD test result, or as a consequence of the use of an IVF/ART device when used according to the manufacturer's instructions for use (user errors reportable under section 5.1.5.1 must also be considered).

means that classification can be carried out by the manufacturer on the basis of case-by-case evaluation and risk analysis. This classification is not related to that found in 2017/745, which is based on the device's intended use.

Tests have to demonstrate the software's function and performance, in other words its ability to fulfil the requirements established at the stage of needs analysis, including measures to minimize major risks and to fulfil regulatory requirements. Accordingly, technical verification must cover:

- design requirements for individual software elements
- their correct integration
- correct functioning of the software system as a whole
- risk minimization requirements.

3.3. Software architecture and modular certification

Stand-alone software can be subdivided according to its user functions, each of these being related to a module. Functions can be medical or non-medical.

Some examples of non-medical function are the following:

- collection and storage of the patient's administrative details
- filing of the patient's medical history.

Some modules can also have ancillary functions, such as:

- audit trail, for reconstruction of events prior to an alarm or audit notification
- access and security, cryptography
- storage and backup of personal data.

The manufacturer must identify the boundaries and interfaces of the different modules, bearing in mind that any module of the software classified as a medical device is subject to certification and regulatory constraints - examples of mandatory MDR requirements being Unique Device Identification (UDI) and post-marketing surveillance.

The limits of modules subject to regulatory requirements for medical devices must be clearly identified by the manufacturer, on the basis of intended use.

If modules subject to regulatory requirements for medical devices are intended for use in combination with other modules within the overall software structure, or with other devices or apparatus, the entire combination must ensure fulfilment of at least the intended function - e.g., a middleware for communication with the hospital system, while not a medical module in its own right, performs its function in combination with the medical module.

These functions must be guaranteed by the software, but are not subject to the life-cycle control requirements set out in IEC 62304: it is nevertheless mandatory to ensure both safety and performance for the overall combination. For example, the module for storage and backup of personal data must guarantee full traceability of the patient.

The manufacturer must evaluate, on the basis of risk analysis, whether segregation measures for the different software modules must be implemented. Segregation is a way of guaranteeing that the software elements do not interact with each other unpredictably, the aim being to avoid side effects from interrelations in the control flow, data flow and access to any shared resources. Segregation works on three different levels:

- Functional: separation of software functions into different modules (e.g., use of middleware);
- Physical: ensuring physical separation of the resources used, by allocation of modules to different hardware units and use of non-shared resources;
- Logical: separation of virtual resources (e.g., use of two different databases).

Segregation makes it possible to establish a separate classification for the different modules that make up the software system, while minimizing propagation of any malfunction together with the associated risk.

The standard makes it possible to use an approach that is at least partly black box in nature, and to carry out tests in a simulated environment. Tests must be performed in *ad hoc* validation environments, for all the software's functional and performance features. For example, it will be possible to create case scenarios representative of typical inpatients in a typical clinic.

The software validation method for regulatory purposes can thus be organized as follows:

1. Identify the validation environment as one in which clinical conditions are simulated on the basis of representative cases, appropriate to the type of clinical use scheduled, as in the following examples:

a. creation of an "average patient", based on data in the literature, characterized by descriptive parameters (clinical anthropometric, phenotypic, behavioural) as identified by a mean-based approach;
b. creation of a "typical" patient, based on data in the literature, characterized by descriptive parameters (clinical, anthropometric, phenotypic, behavioural) as identified by a mode-based approach;

c. creation of a worst case scenario clinical environment - for example, equipped with hardware fulfilling the bare minimum technical requirements.

2. Test software characteristics: in this case, the standard allows a black box approach and requires testing of functional characteristics, risk minimization measures and usability, as well as running a number of typical tests for the device concerned (e.g., installation testing, retrieval from cloud storage). Tests must obviously be repeated for all cases within the purpose-built, simulated environment.

a. Describe the typical flowchart for use of the software. For each functional block (or activity or task), black box testing must be carried out to ascertain that the software can provide a pre-declared and expected deliverable, in terms of the software's possible interactions and/or output.

b. Integrate ISO 14971 and ISO 80002-1, in order to obtain a list of risks requiring minimization; identify the software characteristics that minimize risk, and subsequently add to the functional tests a number of specific tests to demonstrate correct functioning of minimization measures.

c. Use an approach based on IEC 62366 to test product usability, typically by establishing a list of tasks and focusing on the main ones with user tests.

d. For other specific tests on the product, it can always prove appropriate to describe the functional block beforehand in a flowchart and then test the block, using a black box approach.

3. In the event of failure of one or more tests, investigate the causes with a white box approach, in other words testing implementation of the individual software unit only on the functional block or minimization measure concerned. For example, in the event of an alarm function failing for a vital parameter flagged at a pathological threshold level, investigation should be based on analysis of the software structure: check that the data item correctly completes all the scheduled transformations, and identify the operation or code section responsible for the failure.

3.4. A particular case: machine learning

Machine learning comprises all data-driven techniques for creation of learning- and automatic optimization-based prediction or classification models. By extension and metonymy, the term "machine learning" is also applied to

information systems that integrate predictive models created by this technique.

A model's performance depends on at least two key aspects of design and construction: on the one hand, architecture and training methods; on the other hand, quality and quantity of data. All data used in training must be correctly organized and distributed, so that training can produce a mathematical model adequate for the real data that the software will then be used to analyse.

In the case of models devised and developed to help diagnosis[**], data in the training dataset must also be correctly classified (e.g. physiological vs pathological), so that artificial intelligence can be trained to carry out correct classification.

In order for the algorithm to be as safe, efficient and effective as possible, the training dataset must present the best possible characteristics in terms of quality and reliability. To achieve this objective, data identification must be as clinically correct as is always expected of ground truth data.

There is, however, no universally accepted definition of "clinical truth", especially in cases where the data item is not produced by a device or a sensor. Far more often, a single, clinically relevant datum regarding an individual patient can be subject to differing interpretations by different doctors, according to their experience or technological literacy: the higher this so-called observer variability, the lower the inter-rater agreement.

Software performance comparable with that of the most skilled human decision-makers may be achieved by training artificial intelligence, with data based on diagnoses and clinical decisions provided by an appropriate number of doctors (at least three, recognized by the scientific community as very experienced or as key opinion leaders - KOL), and with a proven track record for correctly addressing patients' needs and in terms of patient satisfaction.

Correct identification of KOL in terms of skill, knowledge, experience and other characteristics makes it possible to enhance the reliability of the overall result. In some cases, geographical distribution of the experts concerned must also be factored in: European guidelines can be different from US guidelines, while some ethnic groups can be more prone to certain diseases than others, and so on.

[**]Consistent with definitions used in the MDR, which includes prognosis and prediction in the definition of medical devices, models of this kind are to all intents and purposes medical devices and therefore require certification based on the appropriate classification.

For validation of machine learning-based models, the following approaches are useful:

- assess "clinical truth" by comparing the opinions of different KOL on the same data item, giving "truth" status only to a view on which there is complete agreement, or statistically significant consensus (e.g., based on statistical tests like chi-square distribution), or sufficient agreement (in other words, above a certain statistical threshold like Krippendorff's alpha coefficient);
- create a validation dataset representative of the training dataset in terms of variability and distribution of data regarding the target patient population, or make it as different as possible from the training dataset in order to allow performance assessments in variability-related worst case conditions. Representativeness can be assessed in terms of similarity between datasets by means of statistical tests, such as the multivariate Kolmogorov Smirnov test; in this case, a validation dataset suitable for a worst-case scenario will be associated with a *p* value lower than a given threshold - either 5% or, even more conservatively, 1%. Validation performance below a minimum acceptable accuracy threshold (to be defined on a case-by-case basis) may suggest the need for retraining of the model on more up-to-date or complete data, with a view to their use in continuous monitoring of quality and so-called techno-surveillance of on-market machine learning models;
- maintain a rigid separation of validation and training datasets - in other words, ensure that there are no data in common between the two, and that no transformations (e.g., normalization, standardizations) are made to both on the basis of statistical parameters for only one of the two. This separation of the two datasets, a means of avoiding so-called data leakage, can be achieved by cross-validation techniques such as leave-one-out approaches, provided that precautions are taken to separate the two for every training and performance testing iteration.

The last point is necessary in order to guard against the risk of software malfunction being masked by self-referential validation or, in other words, of the software's classification performance being invalidated by recognition of data that have already been learnt (a phenomenon known as overfitting).

Among suggested criteria to be fulfilled for compliance with the above indications are the following:

- build validation and training datasets with the same inclusion and exclusion criteria;
- build validation and training datasets representative of the same

range of values for parameters associated with the patients included in the dataset (e.g., gender and age distribution, if these are relevant factors for the setting concerned);

• build validation and training datasets representative, where appropriate, of variability in the real patient population, but balanced as far as possible in terms of the classes considered.

Definition of datasets according to these requirements would make it possible to identify the dataset population as the target population for the clinical benefit expected from the medical device, and confirm the suitability of the software for the entire target population. To the same end, the software's accuracy should also be evaluated by nested cross-validation, making it possible to report accuracy data in terms of proportion of errors and corresponding confidence intervals. The rationale here is that these provide an idea of how far the result obtained on a sample of clinical cases from the reference population can be generalized to other samples from the same population.

Compliance with the above indications makes it possible, at least for functional tests, to treat the software as a black box given the task of classifying a dataset, the clinical truth of which has previously been ascertained by traditional methods. Functional validation can be considered successful if running a test set on the software achieves or surpasses minimum acceptable accuracy, a reference level that can be determined on the basis of the performance required from the device. In particular, determination of minimum acceptable accuracy will also have to depend on assessment of the impact any errors will have on the patient's health. Finally, a valid basis for its determination can be state-of-the-art specialist literature, based solely on sources covering comparable patient populations. An important consideration in this respect is that performance values will be closely dependent on the data used for validation, which could be identical only if publicly available. After validation, it will be possible to analyse item by item any discrepancies between the doctor's preliminary evaluation and that given by the software. This analysis can then be used for a further training iteration, in an approach known as active learning.

It should be noted that, in the case of machine learning-based models, clinical validation in a simulated environment will involve considerable difficulties. Often, data based on the literature are either not present or not identifiable; possibly they are available in formats that are difficult to process, unrepresentative of the population or skewed by different biases (e.g.,

selection, gender, age, ethnic group). In addition, validation on an average case basis would give no guarantee of the technology's usability with a real population. In this respect, the worst case is not necessarily a technological limitation related to acquisition of the data for analysis, but may be that of an individual differing considerably from the average patient.

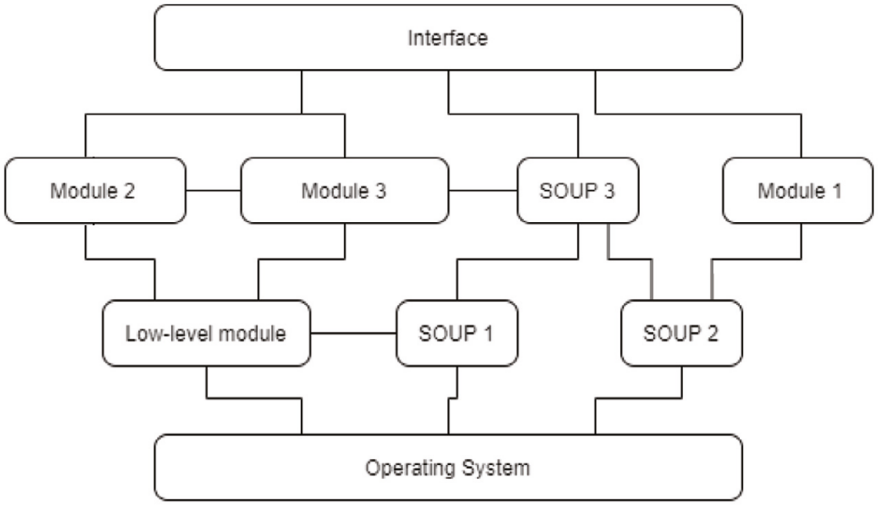
Appendix

A.1 Illustrative definition of software architecture and modular certification

The following is an illustrative example of an IT system diagram comprising three main levels *(Figure 1)*:

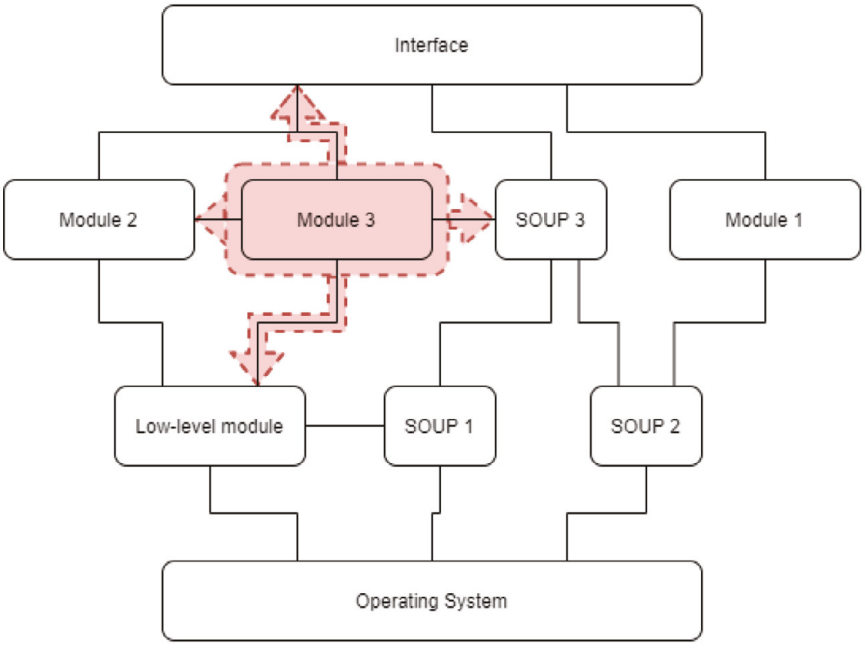
- a level dedicated to interface management between the operating system and the rest of the software;
- an intermediate layer, organized in modules with module-specific software, at least one module being for medical use;
- a top layer, containing the graphic interface and other elements used for module-to-module "connections".

Figure 1 - Example of an IT system divided into modules



As a concrete example, the above diagram could include an Android app, with enabling SOUP for detection of position, the screen access PIN code and connection to a smartwatch. The app includes self-tracking wellness modules, like a pedometer (module 1) and a sleep tracking function (module 2). Module 3 is functionally different, qualifying as a medical device since it detects epileptic attacks. For the "medical" module, functional limits must be clearly identified - e.g., (by segregation) all functional performance features listed in the system's scheduled use are managed by module 3. In any case, design constraints for module 3 will have repercussions on other modules or other levels: a case in point is risk analysis, with possible implications for other modules, for the basic levels and for the main graphic interface *(Figure 2)*. If the system contains SOUP affecting or enabling the medical module, medical device design constraints apply.

Figure 2 - Example of risk propagation in an IT system



Conclusions

DTx design must comply fully with the essential requirements typical of medical devices. Knowledge of regulatory requirements for this category of devices makes it possible to have a prior understanding of the importance of software modularity, a fundamental consideration in terms not only of risk and change management but also of critical issues with software of unknown provenance (SOUP) and approaches to their management.

By contrast, there is no consensus to date on how to deal with various aspects of DTx development, such as incremental learning in artificial intelligence and verification in a simulated clinical environment. Incremental learning can be seen both as an opportunity for continuous enhancement of performance and a threat of divergent performance outcomes; while the importance of correctly addressing verification in a simulated clinical environment is recognized in terms of its safety implications, but has yet to be codified in a universally accepted manner.

In this setting, the authors propose integrated test planning to include simulated clinical verification, usability evaluation and verification of risk minimization measures, with a combination of white box and explainable artificial intelligence approaches in the technical validation of the various software elements. This makes it possible to guarantee that patients involved in the clinical validation phase will be exposed to the safest device possible, while also allowing effective risk monitoring.

What is known

- The concept of modular architecture, and its importance in terms of risk and change management
- Management of software of unknown provenance (SOUP).

What is uncertain

- Management of incremental learning in artificial intelligence
- Management of verification in a simulated clinical environment, to determine all safety aspects before the clinical validation phase.

What we recommend

- Integrated test planning, inclusive of simulated clinical verification, usability and verification of risk minimization measures, so as to determine the safety level before the clinical study phase
- As far as possible, use a white box approach
- In creation of artificial intelligence-based devices, use an explainable AI approach, allowing timely identification and mitigation of any risks associated with machine learning algorithms.

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Data protection and cybersecurity in digital therapeutics

1. Data protection profiles in digital therapeutics

Digital therapeutics (DTx) consist of clinically validated software that carries out a therapeutic function. In other words, a DTx product processes incoming data and generates output data that can influence the patient's behaviour, thus providing a clinical benefit (e.g., an app which provides indications to the patient, with a view to addressing sleep disturbances).

In terms of legal classification, DTx come under the heading of "medical devices", pursuant to Article 1(a) of Directive 93/42/CEE (superseded, with effect from May 2021, by the definition of medical device set forth in Article 1(2) of the new Regulation (EU) 2017/745, more often referred to simply as the MDR). Therefore, manufacture and placing on the market of DTx have to comply with the regulatory requirements set out in the MDR.

As regards their intrinsic mode of operation, DTx function by processing data related to the patient's health that come under the heading of "*particular categories of data*" (according to Art. 4(15) of Regulation (EU) 2016/679, also known as the EU GDPR). It will therefore be necessary to analyse the legal profiles related to this type of processing in the light of the GDPR.

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On the following pages, for reasons of space, we will examine only the main issues concerning detailed processing profiles related to DTx, without dwelling on the general profiles set out in the GDPR.

1.1 Roles and responsibilities in data processing

The first question to focus on is the identification of the different roles and responsibilities in data processing. In other words, which natural person or legal entity will be qualified as the data controller? And, downstream from that, where do other roles and responsibilities lie?

Pursuant to article 4(7) of the GDPR, the data controller is the natural person or legal entity that determines the *"purposes and means of processing"* and bears the general legal responsibility for guaranteeing correct data processing.

Based both on general interpretation of the discipline and the recent European Data Protection Board's *"Guidelines 07/2020 on the concepts of controller and processor in the GDPR"* (draft issued on 7 September 2020), it can be stated that the role of the data controller and, in general, all other roles within GDPR cannot be defined *a priori*, but depend on concrete data processing profiles.

In practice, attention must be paid to who concretely determines the purposes of the data processing and its concrete modalities.

Regarding DTx, we can identify two hypotheses:

- In the first hypothesis, the data controller is the healthcare organization or individual doctor who prescribes the DTx.

In this case, the DTx manufacturer will presumably be appointed as the data processor pursuant to Article 28, as the party that stores and organizes the data (though, in this case, admittedly not empowered to define the purposes of processing). However, it should be noted that the DTx manufacturer will nonetheless also qualify as data controller for all closely related processing activities, notwithstanding the role of data processor, and will have to process the data for some purposes that the MDR identifies as the medical device manufacturer's domain - e.g., postmarketing surveillance (Article 83 MDR), analysis of serious incidents and field safety corrective actions (Article 89 MDR).

- In the second hypothesis, the DTx manufacturer qualifies as the data controller and will, therefore, bear full responsibility for all aspects of GDPR compliance. In this scenario, the healthcare organization/prescribing doctor, while not having a specific role with regard to data processing,

will necessarily be able to access the patient's input and output data in order to monitor the continuing implementation and results of the therapy (presumably as parties processing data under the authorization of the data controller or processor, pursuant to Article 29 of the GDPR).

1.2 General principles of data processing

The subject who qualifies as data controller must guarantee that the data are processed in compliance with the data processing principles listed in Article 5 of the GDPR.

In DTx, compliance with these principles presents the following specific features:

a) *Principle of lawfulness*

Data processing can be carried out only insofar as it has a legal basis.

For DTx, processing is carried out on data related to health (which thus, conceptually, fall under the heading "particular categories of data"), consistent with the legal basis found in Article 9 of the GDPR.

It must also be borne in mind that the legal basis may change, according to which subject is identified as data controller.

Indeed, if the data controller is the healthcare organization or the doctor, the legal basis for data processing can be found in Article 9.1(h), which allows health data processing by healthcare professionals (Article 9.3) for purposes of *"diagnosis, assistance or medical processing"*.

On the other hand, if the data controller is the manufacturer of the medical device (a situation for which no legal basis is provided by Articles 9.2(h) and 9.3), the legal basis for data processing can presumably be only the patient's consent (Art. 9.2(a)).

b) *Principle of purpose limitation*

Another linchpin of the system is the principle of purpose limitation. Article 5.1(b) of the GDPR states that the data controller shall define the purposes of data processing beforehand, and that all data processing shall then be carried out for no purposes other than those previously chosen (which must be declared in the information provided to the data subject for informed consent - see point (c) below, 'Principle of transparency').

In the context of DTx, the main purpose will certainly be *"diagnosis, assistance or medical processing"*, and thus improvement of the patient's general state of health. Moreover, this purpose justifies healthcare use, and

thus the legal classification of DTx as a medical device.

However, the data collected can subsequently be used for other purposes, such as post-marketing surveillance of the medical device (Article 83 MDR), the legal basis for which - as already mentioned - can be found in the MDR itself.

Another purpose of data processing could be scientific research (in the broad definition of recital 159 of the MDR). In this case, bearing in mind the different possibities as to who will be the data controller, it will be necessary to define the legal basis for the data processing to which reference is made (e.g., Article 9.2(h), if the data controller for purposes of scientific research is a public body; or to acquire a separate patient's consent, if the data controller is a private sector DTx manufacturer).

An aspect that should not be overlooked is data processing for marketing purposes (of the patient's and/or the doctor's and healthcare staff's data): in this case, the legal basis for the data processing (irrespective of whether the data controller is a health organization or the manufacturer of the device) has to be the patient's consent. To this end, it must be pointed out that individual consent (of the doctor and/or patient) must be freely given (in other words, with no pressure of any sort) and informed (i.e., on the basis of a clear and comprehensible explanation) - see point (c), below, on the principle of transparency.

Finally, a few remarks of specific relevance to data processing by software. As known, software today can in some cases also operate on a self-learning basis (so-called machine learning): sometimes, the most advanced machine learning functions can lead to different data processing aims from those defined when the software is first used. This could, conceivably, give rise to a scenario of data processing for aims that have no suitable legal basis.

In this regard, it seems appropriate - especially in cases like that of DTx - that software running on a self-learning basis should be programmed so as to prevent its escaping human control.

c) *Principle of trasparency*

In the GDPR system, great importance is given to the principle of transparency. The data subject (in our case, the patient using DTx) is always and in any event the "owner" of their own data - hence the requirement that s/he shall be enabled to understand exactly *how* and *why* their data are being processed, so that s/he can take an informed decision in this regard.

Moreover, the principle of transparency set forth in Article 5.1(a) is

further developed in greater detail in Articles 12 *et seqq*. of the GDPR; in particular, Article 13 deals with the information to be provided to data processing for acquiring an informed consent.

In providing this information, the data controller is required to clarify to the patient the purposes for which the data are being processed, and also how the process itself is carried out (including data storage and an indication of the country where data are to be transmitted and/or stored).

In DTx, run by means of software, a number of profiles are worthy of attention. First of all, Article 13.2(f) establishes that the data controller shall provide the data subject with information about *"the existence of automated decision-making, including profiling, referred to in Article 22(1) and (4) and, at least in those cases, meaningful information about the logic involved, as well as the significance and the envisaged consequences of such processing for the data subject"*.

Even though DTx can arguably not be considered an automated decision-making process in the strict sense of the term used in the GDPR (since either a doctor or a healthcare professional is always involved in the processing), the delicate nature of the type of processing concerned requires that the data controller acts in the most transparent manner.

In this regard, help is provided in recent guidance issued by the *Information Commissioner's Office* (ICO), the UK authority for upholding information rights in the public interest. While the document's clear relevance to artificial intelligence software is readily apparent in its title, *"Explaining decisions made with AI - Draft guidance for consultation"*, it can also be seen as an excellent source of best practices for software not falling within the AI category.

Very briefly, in the above-mentioned document, the ICO specifies that the data controller shall decide how to structure and communicate the information to be provided to the data subject, bearing in mind the following elements: 1) the sector in which the AI model is used; 2) the impact on the individual; 3) the type of data processed; 4) the urgency of the decision; 5) the subjects for whom the information is meant.

The information concerned can, according to the ICO, be divided into two macro-categories:

a. *process-based* explanations: according to which it is necessary to explain that all best practices on software design have been followed in the course of the decision-making process;

b. *outcome-based* explanations: according to which it is necessary to clarify the result of the specific decision, using simple and readily under-

standable language to provide information on the reasoning followed.

Finally, the ICO lists six types of information that, according to the specific case, can either fall under the *process-based or outcome-based* heading. Indications and checklists are also provided, to enable full and correct implementation in this regard.

Very briefly:

1) *Rationale explanation*: the reasons that have led to a decision should be explained, in an accessible, non-technical manner;

2) *Responsibility explanation*: it should be explained who is involved in an AI system's development, management and implementation, and who may be contacted for a human review;

3) *Data explanation*: an explanation must be provided as to which data have been used in a given decision, and how they have been used;

4) *Fairness explanation*: the basics of the software's operation, and how it guarantees fairness in data processing, should be explained.

5) *Safety and performance explanation*: information must be given about how the software works, illustrating its accuracy, reliability, security and the robustness of its decisions.

6) *Impact explanation*: specific information must be given on the steps taken, during an AI system's design and implementation, to take into account and monitor impacts on an individual and on society at large, resulting from the system's use and the decisions it takes.

As already mentioned, while the above indications are not mandatory, they are best practices recommended by the ICO for information to be provided to data subjects in relation to artificial intelligence. They can, of course, also be applied to software not definable as AI.

Finally, with regard to the means of providing the necessary information to the patient, which for DTx might be an app, useful sources are the WP 29 documents "Guidelines on transparency under Regulation 2016 679" and "Opinion 02/2013 on apps on smart devices", as well as the *European Union Agency for Cybersecurity* (ENISA) document *"Privacy and Data Protection in Mobile Applications"*.

d) *Principle of fairness*

Another principle to be upheld by the data controller is fairness, in relation to the data subject's reasonable expectations regarding data processing.

In our opinion, the data subject's reasonable expectations overlap with many aspects of software developer ethics. On that basis, compliance with

the principle of fairness for data processing as set out in Article 5 of the GDPR basically aligns with compliance with the ethical requirements of data processing.

This view finds corroboration in the ICO's *"Guidance on AI and Data Protection"*, particularly in the following extract from the section entitled *"How do the principles of lawfulness, fairness and transparency apply to AI?"*:

"…. if you use an AI system to infer data about people, in order for this processing to be fair, you need to ensure that:

- *the system is sufficiently statistically accurate and avoids discrimination; and*
- *you consider the impact of individuals' reasonable expectations."*

In the Italian setting, useful information in this regard can be found in the document *"Mobile-health e applicazioni per la salute: aspetti bioetici"*, covering bioethical concerns related to mobile health and health apps. This document was issued on 28 May 2015, by the *Comitato Nazionale di Bioetica* (National Bioethics Committee).

e) *Principle of data minimization*

The principle of data minimization calls for limitation of data collection and processing to such data as appear to be necessary in relation to the purposes stated in the explanation provided to the data subject. Compliance with the principle of data minimization is thus not an abstract or predefined issue, but it is closely linked to the purposes of data processing as stated by the data controller in the explanation provided to the data subject.

For illustrative purposes only, it is worth bearing in mind that the information collected and then processed could differ according to whether the purposes of data processing are limited to diagnosis and treatment, or also extended to marketing.

Accordingly, reference must be made to the stated purposes of data processing, so that it can be decided whether the information collected (in other words, "data") is indispensable for their achievement.

f) *Principle of data accuracy*

For processing carried out by software, the principle of data accuracy as stated in Article 5 of the GDPR takes on particular importance. This principle establishes, in general terms, that every data item processed must be accurate and up-to-date, and that all reasonable and necessary measures shall therefore be taken for rectification of inaccurate data.

In the specific field of software (and thus of DTx), data accuracy must

be seen both as an initial necessity and as a final aim, thus including accuracy in operation of the software itself: in other words, accuracy must be the leitmotif throughout the entire data path. There is no question that, if the input data are not accurate or correct, the entire process will be invalidated, and the software's output data will prove inaccurate.

Moreover, with regard to DTx, this concern is particularly relevant in terms of liability - whether product liability in relation to medical devices, or medical liability of the organization/doctor administering DTx. Inaccuracy of output data could invalidate the processing decisions, and thus jeopardize the patient's health and security.

Data accuracy has an even greater impact where software operates on the basis of machine learning and artificial intelligence systems.

g) *Principle of data storage limitation*

Finally, the GDPR states that the duration of data storage should not extend beyond the time at which the purposes of data collection are achieved. In DTx, given that the data are used for medical treatment, it is deemed appropriate that the length of data storage is governed by the same rules as for storage of medical records (in cases where the data controller is a public healthcare organization), or is at least 10 years (if not more), *inter alia* with a view to preserving evidence of possible civil, penal and administrative liability.

1.3 Automated decision-making process and profiling

A further point that should be briefly illustrated is automated individual decision-making and profiling, as dealt with in Article 22 of the GDPR. This has already been referred to above, under the heading "Principle of data transparency", in relation to information to be provided to the data subject.

For reasons of brevity, we intend here to focus solely on Article 22 of the GDPR, which states: "The data subject shall have the right not to be subject to a decision based solely on automated processing, including profiling, which produces legal effects concerning him or her or similarly significantly affects him or her".

The *Article 29 Data Protection Working Party* (WP) document, "*Guidelines on Automated individual decision-making and Profiling for the purposes of Regulation 2016/679*", defines "automated individual decision-making" as "*the process of making a decision by automated means without any human involvement. These decisions can be based on factual data, as well as on digitally created profiles or inferred data*."

Strictly speaking, it can thus be argued that DTx does not come under the heading of "automated decision-making process", in that the decisions taken (which affect the patient's legal sphere) can hardly be defined as automatic and are mostly taken with the involvement of a healthcare professional.

On the other hand, it is understood that, where the software output can be considered to have an automatic effect on the patient's legal sphere and there is no direct involvement of a healthcare professional, the provisions of Article 22 can be fully applied. In particular, the processing modalities in this case require an ad hoc consent.

With regard to profiling, it should be pointed out that the GDPR deals with this aspects of data processing only in Article 22: consent in this regard seems to be required only if there is automated processing.

1.4 Impact assessment

Article 35 of the GDPR states that, where data are processed by the use of new technologies and the data processing involves high risks for the data subject's rights, the data controller shall carry out an impact assessment beforehand.

Basically, this is a document that must contain:

- a systematic description of the intended forms of processing and their purposes;
- an assessment of the necessity and proportionality of processing, taking into account its purposes (and thus evaluating the risk-benefit ratio);
- an assessment of how the data processing could impact the data subjects' rights (e.g., the right to health), and of related risks in terms of impact.

Data processing by DTx requires prior impact assessment, because carried out by software and likely to have a significant impact on the patient's health.

Finally, in the light of the overview offered on these pages, it should be pointed out that the data controller, when carrying out an impact assessment, can decide to ascertain the opinions of the data subjects or their representatives with regard to the scheduled data processing.

2. Security and integrity of data in DTx

The MDCG[1] and IMDRF[2] documents provide an overview of cybersecurity risks for medical devices and indicate the good practices to be adopted to guarantee data security during the design, implementation and post-production phases of a generic medical system or application.

In particular, the MDCG guidance presents cybersecurity requirements for medical devices as stated in European law, addressing specifically such concerns such as the efficacy of data security measures, risk analysis and management throughout the medical device's life cycle and, as already seen above, data protection and data management. The IMDRF guidance sets out principles and practices to manage medical device cybersecurity, with a view to guaranteeing full compliance with European regulatory requirements. Both documents present a systematic examination of practices to be adopted, starting with fundamental definitions in the field of information security before dealing extensively, but in general terms, with the management of risks and threats. While extensive, the two documents do not provide specific indications regarding DTx cybersecurity requirements, but they are limited to setting out such requirements for medical devices in general.

In addition, the perspectives of both documents are necessarily of an indicative nature, so that they can be exhaustively applied to different possible types of medical devices. However, if the approach to data security has to be contextualized in greater detail by applying its principles to DTx, the discussion has to be less abstract, and a more detailed approach has to be developed. The specificities of DTx need to be examined in detail and, in a certain sense, raise different issues from other medical devices. This becomes clear if one thinks of the difference between a classic medical device, such as an infusion pump for chemotherapy, and a DTx service available as used on a patient's smartphone. Without taking into account the possible complexity of the software in the two types of device, the DTx manufacturer does not have the simple option of being able to use a trusted hardware support, because the patient's personal smartphone is inevitably exposed to further threats: this means that the attack surface is far greater than in the case of the classic medical device. The extent of this vulnerability to threats in the case of DTx must be considered during the research phase, and also in risk analysis and management.

For a full understanding of this difference from other medical devices, we will now examine the architecture of a generic DTx application (or SaMD - Software as a Medical Device), before analysing insider threats and outsider threats. This will facilitate the description, based on an example, of useful concepts and practices to ensure cybersecurity in the context of DTx.

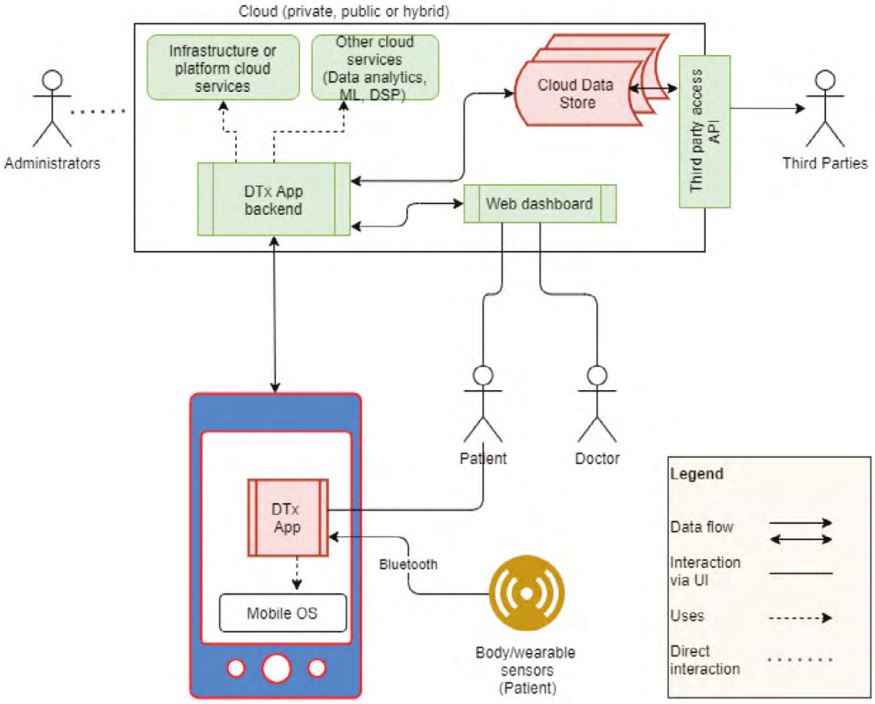
2.1 Reference architecture

The general reference architecture for a system delivering a DTX service (DTx[3] or SaMD) can be outlined as in *Figure 1*.

The DTxApp, the chief means of access to DTx, is made up of two main macro-components:

- The first, the DTxApp, is hosted and run on the patient's mobile device. Below, we will assume that the DTxApp has been developed using a Cross-platform or Hybrid web pattern[4].
- The second component, the DTxApp backend, is hosted and run on a cloud platform and can perform several functions, such as access to data memorized in the Cloud Data Store (CDS), writing of data in the CDS, analysis or processing of data, execution of DTx algorithms, and execution of engagement algorithms. The DTxApp backend offers a series of Application Programming Interfaces (API), to be used by the DTxApp and the Web dashboard.

Figure 1 - Reference architecture of a delivery system for a DTx service



The Web dashboard is a web portal that typically enables access to a subset (or an overset, according to the role of the person accessing it - e.g., patient, caregiver or doctor) of functions offered by the DTxApp.

The cloud, which can be public, private or hybrid according to needs, can host and run other support services - e.g., authentication, user profile and therapy profile management, access/memorization of dynamic data, data analytics, voice recognition and image recognition, monitoring, data stream processing (DSP) and many others. It is important to bear in mind that the CDS, storing patient treatment data, should be managed by a cloud provider with specific features for health data management, or certified for this purpose (e.g., HIPAA, HITRUST CSF, ISO/IEC 27018).

Finally, the DTx/SaMD could offer third-party access API, as in the figure, thus allowing third party systems to access the data collected (e.g., Ministry of Health, pharmacies, pharmaceutical companies manufacturing and distributing traditional drugs to be combined with DTx systems).

Below is a list of the actors interacting with the system:

- The patient is the subject who accesses the DTxApp, using the personal mobile device on which the app is hosted. The app provides the patient with a user interface (UI). Typically, it also enables monitoring of certain vital parameters, by means of implantable/wearable body sensors. In addition, the patient can interact with the DTxApp through the web dashboard - e.g., via a PC.
- The caregiver is the contact person who normally provides day-to-day support for the patient. This is the person who answers calls, reminds the patient of therapies, accompanies him/her throughout the diagnostic-therapeutic and clinical pathway, and takes charge of daily care. The caregiver too accesses the DTx/SaMD system by means of a DTxApp or web dashboard.
- The doctor accesses the system via the web dashboard, to check the patient's state of health and the progress of treatment.
- The healthcare professional (nurse, speech therapist or other healthcare operator), on the basis of a doctor's prescription, takes care of any needs and/or actions identified by reading the data transferred. The healthcare professional accesses the DTx/SaMD system via the web dashboard.
- Third parties are subjects (e.g., pharmacy, manufacturer of drugs used in combination with DTx, Ministry of Health) who can access data, typically in aggregate form and anonymized by means of a dedicated API.
- Administrators, not examined here, are the subjects tasked with management of the DTx/SaMD cloud platform.

In order to understand possible cyber threats, it is also important to

provide a brief explanation of how the various DTxApp system components interact. Again using the architecture in *Figure 1* for illustrative purposes, from bottom to top:

- The body/wearable sensors provide data to the DTxApp via Bluetooth or another wireless protocol;
- The DTxApp, installed and run on the patient's mobile device, uses the operating system functions (Android or iOS) for access to resources (e.g., local memory) and I/O operations (e.g.,, use of the internet, display, audio or camera);
- The DTxApp communicates with the DTxApp backend to carry out such procedures as authentication, access to the user profile and therapy, access to dynamic data, sending of data generated by sensors or by the DTxApp, etc. Interaction between the DTxApp and DTxApp backend takes place via the internet, usually by means of web services (API REST);
- The DTxApp backend uses cloud platform services to guarantee performance, reliability and security - e.g., load balancing, scaling of resources, geographical distribution, redundancy, VPN, firewall, etc.
- The DTxApp backend, in turn, can also use cloud services such as authentication, user profile management, data encryption and scalable platforms for data analysis (e.g., Hadoop) or for data stream processing (e.g., Spark);
- The DTxApp backend reads and writes data from one or more CDS;
- The web dashboard uses the API provided by the DTxApp backend for web access to DTxApp functions.

2.2 Threat analysis

The cyber threats to the DTx system mentioned above will now be analysed.

Many of the DTx/SaMD system components in *Figure 1* (the ones indicated in green) can be made secure by using good practices and standard technologies, as illustrated in the MDCG and IMDRF documents. In particular, technological solutions and security checks are available for communication networks and protocols (ISO/IEC 27033 Parts 1-6 inclusive), cloud services (ISO/IEC 27017) and applications carried out on the cloud as an integral part or supporting element of DTx. On the other hand, the DTxApp (run on the user's mobile device) and the CDS (in red in *Figure 1*) are the weak links in the system and merit closer analysis.

2.2.1 Main threats to the Cloud Data Store component

The Cloud Data Store (CDS) is certainly one of the most enticing resources for anyone wishing to attack the system[5]. As shown by Tang *et al.*[6],

a CDS can be subject to various types of threat - e.g., data theft or disclosure, illegal access, corruption or loss of data, and violation of data protection. The culprits can be hackers, curious cloud service providers (who can readily view users' data and access profiles), or vulnerable cloud service providers who can lose or compromise data. Recently, the scientific community has proposed a number of techniques to make CDS secure, but such solutions are still immature. In addition, the techniques to be used are closely dependent on the specific use of the CDS and the security requirements.

For example, if research must be carried out on the data without affecting their confidentiality, encryption techniques are recommended. These make it possible to search for information inside an encrypted database (searchable encryption)[7]: only the final result will be decrypted. On the other hand, if the intention is to guarantee the confidentiality of data during their processing by means of an application (e.g., DTxApp backend, or third party applications), homomorphic encryption techniques should be used[8]. These make it possible to perform calculations on encrypted data without having to decrypt them. If the DTx provider is interested in sharing data with third parties, doctors and patients, data access and data integrity must be at all times controllable. This means that controlled access must be ensured, by means of innovative protocols such as the following:

- selective encryption[9], enabling selective access to encrypted data by advanced encryption key management techniques;
- attribute-based encryption[10], meaning a technique to manage access policy for encrypted data on the basis of users' privilege levels (e.g., doctors, patients, third parties, administrators);
- provable data possession[11], enabling the provider of the DTx/SaMD service to verify that the data memorized in a CDS are correct (useful when the CDS it not under the control of the DTx/SaMD provider, but entrusted to third parties);
- proof of retrievability[12], making it possible to verify that a file is intact and always available to legitimate users.

Finally, it is important to consider the problem of data protection and privacy for users requiring access to data memorized in the CDS and to cloud services (DTx/SaMD). Examples of innovative techniques for this purpose include the following:

- access pattern protection[13], to mask the externally observable behaviour of users accessing a cloud service (observation of their behaviour could enable system hackers to garner sensitive user information);

• query privacy protection[14], to mask associations between indexes and keywords used for research and the corresponding data;

• user identity protection[15], ensuring that the identity of the user accessing data remains secret (following authentication).

2.2.2 Main threats to the DTxApp component

Security practices included in the MDCG and IMDRF documents, though generally recognized as effective, can find their full application in infrastructure that delivers a DTx service, as long as there is complete control of every single component shown in *Figure 1*. The main differences between a medical device (MD) and SaMD are the characteristics of the underlying IT infrastructure, and the control that can be kept over it. For a classic MD such as a pacemaker, the manufacturer has the possibility of controlling and certifying every aspect of development - from firmware to communication protocols, the update system and so on; on the other hand, in the case of generic SaMD, security control depends mostly on external factors, related to the operating system (Android or iOS) of the patient's mobile device, thus remaining outside the control of the DTx/SaMD manufacturer.

Specifically, as stated by MDCG in "Practice 4 - Secure implementation", each externally supplied system component must comply with the practices defined in "Practice 1 - Security management", though these seem not enough to maintain a high standard of security for DTx/ SaMD, at least insofar as the security of the patient's mobile device is concerned.

Given the constant increase in malware on mobile platforms, there is an undeniable risk of the patient's smartphone already being compromised before the SaMD is installed. A study by Kaspersky on data collected in the year 2019, for example, identified 3,503,952 malicious installation packages, 69,777 new mobile banking Trojans and 68,362 new mobile ransomware Trojans on clients' mobile devices (16).

This possibility, not covered by the MDCG and IMDRF documents, deserves particular attention because the level of risk involved is not negligible. A possible objection is that a similar level of risk is present even with equally sensitive applications such as those used by banks for personal finance, but it is readily apparent that the two situations are rather differently managed. Where a smartphone hosting a banking app is compromised, a would-be hacker will in any case always have to interface with the bank's systems, since all financial information is stored and managed sole-

ly by them; the application is merely an interface for the user. For this reason, the bank can always notice any unusual activity, blocking it where appropriate and reporting it to the user and the authorities concerned: bank operations must in all cases be approved by the bank server. By contrast, in SaMD, the patient follows the treatment and provides inputs (if required) to the DTx application, generally with no need for the DTxApp backend's constant validation: the patient's mobile device enables direct interaction with the DTxApp. This first example serves to illustrate the difference between SaMD and any other medical device, as well as any other App used today, in terms of cyber risk management.

It is useful at this point to consider two cases. In the first, malware has already been installed and taken complete control of the patient mobile device, with the result that the therapy administered to the patient is not as intended. Since the malware has complete control over the patient's mobile device, it can also show the cloud control system that everything is normal and the patient is improving. As many SaMD systems currently use mechanisms similar to cognitive-behavioural psychotherapy, a deliberate change of these therapies in the treatment of serious conditions such as drug addiction could aggravate the problem.

In the second case, instead of modifying the content of the medical treatment administered, the malware alters the patient's inputs and responses to the DTxApp. This means passive alteration (in other words, without modifying the DTx software) of the patient's treatment pathway. Some SaMD systems adapt the medical treatment according to progress made, changing its objectives if - and when - certain results are achieved. Inducing this type of system to think that certain aims of the medical treatment have been achieved could thus, for example, bring about a premature change in the treatment given to the patient, compromising its efficacy or even worsening the patient's condition.

These examples show how, in the case of SaMD, normal security practices as described in the MDCG and IMDRF documents are not enough, meaning that specific further actions are needed to mitigate the peculiar threats and risks described above. Among possible solutions could be device attestation of the patient's mobile device or the DTxApp[17], and integration of encryption systems for the cloud control system to validate the SaMD's delivery of treatment. DTx/SaMD should also be fitted with anomaly detection mechanisms, for automatic or semi-automatic detection of anomalies in administration of the treatment and in the individual's re-

sponse to it, as previously mentioned. If the patient's data are compromised from the very outset of treatment, however, it is important to recognize that this could make it impossible to identify the anomalies, given the lack of correct data on which to base decisions. Hence the need, in suspect cases, for an independent, trusted, direct and frequent channel of communication with the patient, to confirm the state of progress in treatment and the real extent of the resulting improvement or worsening. This channel could be set up by extending functions of the control room in which healthcare professionals work, enabling a response to patients' and caregivers' doubts about any change in the treatment schedule. In this case, operators answering telephone calls must be able to speak the necessary languages correctly and understand what the patient/caregiver is reporting.

2.3 Concluding remarks

In conclusion, DTx are associated with risks in relation to cyber threats that have to be specifically assessed and limited, paying particular attention to the specificity of DTx/SaMD as a mixture between a medical device and software distributed across a complex architecture. Despite the availability of many technological solutions enabling adequate mitigation of cyber risks, both for medical devices and for software products, it is the very specificity of DTx/SaMD that requires targeted further integration of the practices and principles set out in the MDCG and IMDRF documents. For example, the template of the ISO/IEC 27000 family of standards could be taken as a basis for practices enabling creation of an information security management system: to enable practical application of the general guidelines and requirements for information security management, which are necessarily very broad since they are devised for adaptation to organizations of any type and size, the standards provide guidelines specific to various settings/sectors (e.g., financial services, cloud services, inter-sectoral and inter-organizational communication, etc.). In addition, to make their application more concrete and readily practicable, the standards also include annexes detailing specific controls and adequate information security management mechanisms. For the DTx/SaMD field, what seems essential is to ensure that the specificities of such systems are methodically addressed in relation to cyber risks, and that there is coordinated development of a specific document setting out security management guidelines for the information processed, together with a series of dedicated controls to be applied throughout the system's life-cycle.

What is known:

- DTx operates by processing data on the patient's state of health, which fall under the heading "particular categories of data" (Article 4.15, Regulation (EU) 2016/679). It will thus be necessary to analyse the legal profiles involved in this type of data processing, in the light of Regulation (EU) 2016/679 (the so-called GDPR). The data controller must guarantee that data are processed in compliance with the principles set out in Article 5 of the GDPR: lawfulness, purpose limitation, transparency, accuracy, data minimization, data accuracy, and limitation of data storage
- Where a DTx/SaMD system is set up, technological solutions and security controls are available for protection of data networks and communication protocols (ISO 27033, Parts 1-6 inclusive), cloud services (ISO/IEC 27017) and applications run on the cloud, as an integral or supporting part of DTx
- Use of DTx depends on a bring-your-own-device policy, meaning that the patient, to access the treatment, must have a device such as a smartphone and the necessary data connection.

What is uncertain:

- The CDS is certainly one of the most enticing resources for a hacker. Among the threats to which a CDS is exposed are data theft or disclosure, illegal access, corruption or loss of data, and violation of data protection. The scientific community has proposed various solutions that are still immature, to guarantee confidentiality, integrity, availability, and protection of data memorized in CDS. This has to be carefully taken into account during design and implementation of a DTx/SaMD system
- The fact that a DTxApp is installed on a mobile device belonging to the user means that the setting is, by definition, not trusted. The implications of this can compromise the efficacy of the treatment or lead to severe undesired effects. Given their intrinsically general nature, the MDCG and IMDRF guidelines do not develop this important aspect.

What we recommend:

- Use of high-level governance guidelines like MDCG and IMDRF must be complemented by specific and detailed technical analysis of the new cyber risk, resulting from a complex mobile device app software in combination with the traditional concept of a medical device. This will enable implementation of specific security controls for DTx/SaMD -

e.g., taking as a template the ISO/IEC 27000 family of standards
- The patient's and caregiver's digital literacy has to be ascertained before prescribing DTx, and tutorials or training courses on the key role played by the patient must be organized.

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Clinical evaluation of digital therapeutics

1. Evaluation of clinical benefit

Since software delivering digital therapeutics (DTx) is classified as a medical device, in Europe it must comply with Regulation (EU) 2017/745.

An important difference between the obsolescent Medical Device Directive (MDD) and the Medical Device Regulation, which came fully into effect in May 2021, is the detailed requirement for evaluation of performance and clinical benefit data. Evaluation of the software's efficacy must be based on clinical data and clinical evidence. This means that it is no longer enough to demonstrate that the software works: there must also be documentation of statistically significant efficacy in providing the clinical benefit for which it was designed. In many cases, it will not be possible to collect sufficient clinical evidence merely on the basis of the literature, and adequate clinical investigation will therefore be necessary.

Developers can refer to ISO 14155 ("Clinical investigation of medical devices for human subjects - Good Clinical Practice"), which details

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methods for planning and monitoring of clinical investigation.

Manufacturers and regulatory authorities can also consult MDCG 2020-1 "Guidance on Clinical Evaluation (MDR)/Performance Evaluation (IVDR) of Medical Device Software", dated March 2020, a source of detailed indications regarding how to plan the various aspects of collecting clinical evidence and how to draft reports for regulatory purposes.

The guidance is particularly appropriate when dealing with diagnosis and monitoring software, whose expected benefit is the availability of accurate information. Regarding clinical evaluation of DTx, we find that the document provides some useful information but should go into greater detail regarding specific modalities.

First and foremost, the definition of clinical benefit is confirmed (Article 2.53 of MDR) as follows: "*[means] the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health*."

The MDR (Article 2.51) also clarifies the definition of clinical evidence (*"clinical data and clinical evaluation results pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer"*).

Another key concept reiterated in the MDCG 2020-1 guidance is that of "valid clinical association", meaning "*the extent to which the (software) output is associated with the targeted physiological state or clinical condition*". This association must demonstrate a robust connection between the scientific principles underlying the software's use and the expected benefit.

Also important in MDCG 2020-1 is the definition of generalizability (*"the ability of medical device software - MDSW to extend the intended performance tested on a specified set of data to the broader intended population"*). The concept of generalizability should be taken into account whether the intention is to create a database for the software's technical and preclinical validation, or to define inclusion and exclusion criteria for clinical investigation - and, more generally, when discussing implementation of a device outside its clinical investigation setting. In terms of planning, in most cases the clinical development of DTx includes an exploratory initial phase (pilot studies), followed by

an investigation phase to produce evidence of efficacy and safety as required for approval in the specific therapeutic indication (pivotal studies for CE certification).

The characteristics of pilot studies and pivotal studies for DTx tend to reflect the pattern typically adopted in investigation of traditional therapeutic interventions (e.g., pharmacological therapy or behavioural therapy); however, the very nature of a DTx intervention may require revision or adaptation of the standard investigation models, in particular with regard to choice of endpoints, indicators of efficacy and control procedures, not ruling out the possibility of creating/validating outcome indicators (clinical, health technology assessment - HTA, etc.) specifically suited to these types of product. One of the main characteristics of DTx is the active participation of the patient/caregiver in the treatment pathway. Based *inter alia* on indications which have given evidence of benefit, the planning of studies to produce evidence in relation to DTx should therefore give close attention to selection and motivation of patient/caregiver, with representatives of both these groups ideally involved from the very outset in definition of the study project[1,2].

2. Overview of existing clinical trials

The aim of this section is to provide an overview of studies designed for development of some medical devices identified as DTx.

To provide a consistent analysis, various aspects have been extrapolated, such as the presence of gold standard comparators, the population from which subjects are recruited, the type of intervention and control, and the definition of primary outcomes.

2.1 Advanced phase products

This section analyses studies that have provided clinical evidence of efficacy for some products in an advanced phase of development and/or already on the market.

The following is a list of studies whose results have been used by manufacturers to demonstrate the efficacy of the solution under investigation, as reported by scientific publications in peer-reviewed journals or registration dossiers on the site *clinicaltrials.gov (Table 1)*.

Table 1 - Overview of advanced phase trials to demonstrate efficacy of various DTx products (Updated April 11, 2021)

Product	Experiment	Patients evaluated	Condition or disease	Intervention	Control	Primary outcomes
reSET[3]	RCT	507	Substance abuse	Reduced standard therapy	Standard therapy	Reduction in substance use (patient-reported outcome and urine)
				Therapeutic Education System (online behavioural therapy)		Time up to cessation of therapy
reSET-O[4]	RCT	206	Opioid dependence	Digital CRA	Suboxone	Abstinence
				Suboxone	CM	
EndeavorRx (previously known as AKL-T01)[5]	RCT	348	ADHD	AKL-T01	AKL-T09	Change in Attention Performance Index
						Change in Test of Variables of Attention score
EndeavorRX (previously known as AKL-T01)[6]	Single arm interventional	203	ADHD	AKL-T01	/	Change in Impairment Rating Scale
EndeavorRx (previously known as AKL-T01)[7]	Cohort study	80	ADHD	AKL-T01	/	Improvement of the Attention Performance Index
EndeavorRx (previously known as AKL-T01)[8]	Cohort study	44	SPD	AKL-T01	/	Improvement of ADHD symptoms
EndeavorRx (previously known as AKL-T01)[9]	RCT	19	ADHD and ASD	AKL-T01	Digital Control	Improvement of the Attention Performance Index
						Improvement of ADHD Symptoms

Noom[10]	RCT	202	Prediabetes	Noom Coach DPP	Standard therapy	Weight change
Clickotine[11]	Single arm interventional	416	Smoking addiction	Mobile Smoking Cessation Solution	/	Number of participants who remain active users
Bluestar[12]	RCT	163	Type 2 diabetes	Coach Coach-PCP Portal Coach-PCP portal with decision support	Standard therapy	Reduction of glycated haemoglobin
Diabeo[13]	RCT	667	Diabetes	Diabeo Diabeo + Telemonitoring	Standard therapy	Reduction of glycated haemoglobin
Sleepio[14]	RCT	120	Chronic insomnia	Cognitive behavioural therapy	Placebo Standard therapy	Sleep efficiency
Kaia COPD[15]	Observational	56	COPD	Digital pulmonary rehabilitation	/	COPD evaluation test
Kaia back pain[16]	Retrospective	180	Chronic back pain	Application	/	Level of pain
Propeller Health[17]	RCT	495	Asthma	Monitoring and feedback	Monitoring	Reduction of beta-agonist use
ProAir Digihaler[18]	RCT	330	Asthma	Albuterol eMDPI DS	Albuterol	Improvement in Asthma Control Test
myCOPD[19]	RCT	60	COPD	Application	Standard therapy	CAT questionnaire
Omada health[20]	RCT	600	Prediabetes	Online diabetes prevention programme	Standard therapy	Reduction of glycated haemoglobin
Happify health[21]	RCT	4485	Depression and anxiety	Happify	Psychoeducation	Questionnaire (PHQ-9, GAD-7)
ATENTIVmynd[22]	RCT	46	ADHD	Feed Forward Modeling	Standard non-pharmacological therapy	ADHD-RS, CGI scale, Quotient ADHD, PERMP, WJ-III

SmartQuit[23]	RCT	2503	Smoking	Smartquit	Application part of standard therapy	Abstinence prevalence of 30 days
Natural Cycles[24]	Prospective	16331	Birth control	Natural Cycles	/	Number of undesired pregnancies
Somryst[25]	RCT	303	Chronic insomnia	Sleep Healthy Using the Internet	Online patient education	Insomnia Severity Index
CureApp[26]	RCT	584	Nicotine dependence	CureApp	Control device	Continuous abstinence rate
DigCog[27]	RCT	60	Multiple sclerosis	Tablet Game	Tablet Game 2	Change in speed of execution
iCanQuit[28]	RCT	2415	Smoking addiction	iCanQuit (Mobile Smoking Cessation Solution, based on CBT)	QuitGuide (Mobile Smoking Cessations, based on National Cancer Institute)	Smoking abstinence
Balance [29]	RCT	244	Hazardous or harmful drinking	Online single session screening procedure + online multi-session follow-up programme (Balance)	Online single session screening procedure + online booklet about the effects of alcohol	Reduction in alcohol consumption
One Drop App With an Activity Tracker [30]	RCT	95	Type 1 diabetes	One Drop App + Activity Tracker	One Drop	Reduction of glycated haemoglobin
Dynamicare[31]	Cohort study	108	Substance use disorder	Smartphone app	Standard therapy	Presence at appointments - Substance use - Duration of treatment
Constant Therapy[32]	RCT	36	Post-stroke aphasia	Constant Therapy	Workbooks	Western Aphasia Battery Revised
MindScience[33]	RCT	65	Anxiety disorders	Unwinding Anxiety phone app & standard therapy	Standard therapy	Uunwinding Anxiety programme management - Penny State Worry Questionnaire

NightWare Therapeutic System[34]	RCT	270	Post-traumatic stress syndrome	NightWare Therapeutic System	NightWare Therapeutic System in Sham Mode	Change in Pittsburgh Sleep Quality Index
Parallel [35]	RCT	558	Irritable Bowel Syndrome (IBS)	Therapist telephone delivered CBT	TAU	IBS symptom severity score
				Web-based CBT		Work and Social Adjustment Scale
						Quality-adjusted life years
Quit Genius [36]	RCT	556	Smoking Addiction	Smarthpone delivered Cognitive Behavioural Therapy	Very Brief Advice along Ask, Advicse, Act model	7-day point prevalence, abstinence at 4 weeks post-quit date
Perx Health [37]	Retrospective Observational	373	Pharmacological treatment	Multi-component digital therapeutic	/	Adherence implementation rate
Sidekick [38]	RCT	146	Obesity	TAU + digital therapeutics	Standard weekly coaching sessions	Change in body mass index
Wellthy [39]	One arm interventional	102	Type 2 Diabetes	Lifestyle coaching app-delivered	/	Change in glycated hemoglobin

The table presents the state of the art as at 11 April 2021. RCT = Randomized controlled trial;
TAU = Therapy as usual (Standard therapy); CRA = Community reinforcement approach; CM = Contingency management;
ADHD = Attention deficit hyperactivity disorder; PRO = Patient reported outcome;
COPD = Chronic obstructive pulmonary disease; IBS = Irritable bowel syndrome; SPD = Sensory processing dysfunction.

It can be seen that for products in an advanced phase of development, many have been tested in randomized controlled trials (RCT), with at least 200 patients evaluated. For primary outcomes, items considered include physiological parameters, patient behaviour, or results of validated questionnaires. For the control group, there is a preference for therapy as usual or for administration of a digital placebo, to all intents and purposes "analogous" to the concept of placebo as usually understood in the RCT setting. By digital placebo is meant a digital solution comparable with the DTx being tested, in terms of content (the placebo carries all the information provided by the DTx, but using static rather than interactive interfac-

es) or in terms of graphic presentation (it presents the same interfaces and introduces the same user routine, but without the elements responsible for clinical benefit).

2.2 Development phase products

There are many examples of DTx currently in the development phase. The following is a list of these, in both completed and ongoing studies, and as registered on the site *clinicaltrials.gov (Table 2)*.

Table 2 - Overview of development phase studies to demonstrate efficacy of DTx products (Updated April 11, 2021)

Product	Experiment	Participants	Condition or disease	Intervention	Control	Primary outcomes	State
MyDiPP[40]	RCT	200	Prediabetes	MyDiPP	Standard therapy	Weight loss	Recruiting
One Drop[41]	RCT	500	Prediabetes Type 1 diabetes Type 2 diabetes	One drop	Standard therapy	Change in A1c	Ongoing
MyMee[42]	RCT	50	Lupus erythematosus	MyMee	No intervention	Brief Pain Inventory-Short Form Functional assessment of chronic illness therapy-fatigue LupusQOL	Ongoing
Ibis[43]	RCT	240	COPD	Ibis	No intervention	Reduction of intensive care	Unknown
Therapeutic Education System-Native Version (TES-NAV)[44]	RCT	53	Substance use	TES-NAV Standard therapy	Standard therapy	Number of weeks of abstinence	Recruiting

No name declared[45]	RCT	195	Smoking addiction	(Trattamento A)	(Trattamento B)	Smoking abstinence	Recruiting
Fareweel[46]	Single arm interventional	118	Type 2 diabetes	FareWell	/	Level of engagement	Completed
PEAR-004[47]	RCT	113	Schizophrenia	PEAR-004	Sham	Change in Positive and Negative Syndrome Scale Percentage of dropouts	Completed
NightWare Therapeutic System[48]	RCT	400	Post-traumatic stress syndrome	NightWare Therapeutic System	NightWare Therapeutic System in Sham Mode	Change in Pittsburgh Sleep Quality Index	Recruiting
NightWare Therapeutic System[49]	Single arm interventional	400	Post-traumatic stress syndrome	NightWare Therapeutic System	/	Change in Pittsburgh Sleep Quality Index	Recruiting
NightWare Therapeutic System[50]	Single arm interventional	15	Post-traumatic stress syndrome	NightWare Therapeutic System	/	Change in Pittsburgh Sleep Quality Index	Ongoing
Luminopia[51]	Single arm interventional	84	Amblyopia	Luminopia	/	Visual acuity amblyopic eye	Completed
AKL-T03[52]	Single arm interventional	21	Multiple sclerosis	Project: EVO	/	Brief International Cognitive Assessment for Multiple Sclerosis	Completed
EVO Monitor[53]	Single arm interventional	100	Multiple Sclerosis	EVO Monitor	/	Brief International Cognitive Assessment for Multiple Sclerosis	Completed
Limbix Spark[54]	RCT	410	Depression	Limbix Spark	Psychoeducation	Change in depression symptoms	Recruiting
Continuing Care[55]	RCT	100	Substance use disorder	Continuing Care app	Standard therapy	Weeks of treatment	Recruitment pending

iSage[56]	RCT	40	Type 2 diabetes - Diabetic complications	iSage App with glucometer connected	Standard therapy	Change in A1C	Recruiting
ApricityRx[57]	Cohort study	100	Cancer	ApricityRx mobile application	/	Use of app to view educational videos and data reported by patients	Recruiting
Leva Pelvic Digital Health System[58]	RCT	350	Stress-related urinary incontinence	Leva Pelvic Digital Health System	Kegel exercises	Urogenital Distress Inventory (UDI-6) – Bladder diary	Recruiting
Vitadio[59]	RCT	100	Insulin resistance - Prediabetes - Type 2 diabetes - Obesity	Vitadio Health	Standard therapy	Weight change	Recruiting
Cognoa[60]	Single arm interventional	30	Autism spectrum disorders	Cognoa	/	Usability	Recruiting
PEAR-008[61]	RCT	130	Opioid dependence	Digital CRA	reSET-O	Patient engagement	Recruitment pending
DTx for pain software[62]	RCT (3 arms)	100	Chonic back pain	DTx	Sham - Standard therapy	Self-report of disability, Oswestry Disability Index – Objective report of disability	Ongoing
Gotcha! Therapy App[63]	RCT	34	Dementia or Alzheimer	App-based therapy + maintenance app	App-based therapy without maintenance	Change in Gotcha Outcome Measure (GOM) time	Ongoing
iTALKbetter[64]	RCT	34	Stroke/ Aphasia	iTALKbetter advanced (reactive) app-based therapy for post-stroke anomia	iTALKbetter base (deterministic)	Change in accuracy of performance in a specifically designed Word Retrieval Test	Ongoing

No Name Declared[65]	RCT	80	Smoking addiction	App/ Training	Standard smoking cessation app	Change in Blood Oxygen Level Dependent Signal	Completed
BioBase[66]	RCT	262	Anxiety	Mobile App and Wearable device	Delayed intervention	State-Trait Anxiety Inventory	Completed
HERB[67]	RCT	146	Hypertension	Mobile app + standard lifestyle modification	Standard lifestyle modification	Mean change in 24-hour systolic blood pressure	Completed
So-Lo-Mo[68]	RCT	240	Smoking addiction	So-Lo-Mo + Psychological advice + Bupropion pill	Psychological advice + Bupropion pill + Varenicline Pill	Smoking abstinence rate	Completed
Mindful Garden[69]	RCT	70	Delirium	Mindful Garden + standard care	Standard care	Use of unscheduled (PRN) medication	Not yet recruiting
No Name Declared[70]	Cohort Study	100	Diet modification	Igital therapeutic carbohydrate restriction programme	/	The percentage of eligible patients who receive prescriptions to access the online TCR programme	Recruiting
MIRAI[71]	RCT	540	Major Depressive Disorder	MIRAI ver A	MIRAI ver B	Montgomery-Asberg Depression Rating Scale	Recruiting
Zemedy[72]	RCT	44	Irritable Bowel Syndrome	Zemedy + TAU	TAU	Change in IBS symptoms based on the IBS symptom severity score	Not yet recruiting
DART[73]	RCT	50	Parkinson Disease	Augmented reality multimodal training	Traditional multimodal training	Gait velocity	Recruiting
JOGO[74]	RCT	80	Chronic Low-back pain	JOGO Digital Therapeutics EMG Biofeedback	TAU	Change in pain intensity	Recruiting

3. Characteristics of pilot studies

A pilot study or feasibility study is generally a small-scale study, useful in testing whether a project is adequate, assessing its feasibility or obtaining information on the basis of which to determine sample size for more extensive (pivotal) investigation[75].

In the case of medical software, a pilot study can be relevant for:

- demonstration of usability, for the interface or for associated hardware devices (e.g., wearable sensors);
- creation of a training database for artificial intelligence;
- definition, for subsequent studies, of the population to be evaluated (including sample determination), of key study design features such as recruitment, randomization and blinding modalities, as well as primary aim and secondary and/or exploratory endpoints;
- demonstration and quantification of the valid clinical association between outputs delivered by the software and clinical benefit.

Almost all pilot studies are non-randomized and have no control group. In addition, they do not always include efficacy endpoints, while they often focus on safety endpoints.

The following is a brief presentation of two illustrative cases, differing in size and study characteristics.

3.1. Treatment for smoking cessation (Clickotine)

This is an illustrative case of an initial study, conducted on a broad population of more than 400 subjects, to evaluate usability, efficacy and safety outcomes[7].

Clickotine is an app that can be used on a smartphone, designed and developed to deliver the essential elements of the United States programme for smoking cessation (US Clinical Practice Guidelines) - e.g., advice and encouragement regarding smoking cessation, assessment of the will to stop smoking, motivational stimuli, support for planning, links with other interventions (counselling, pharmacological treatment, social support, dedicated phone line), follow-up.

Results of a single-arm 8-week initial study were published in 2017. The outcomes measured were the subjects' engagement (number of times the app was opened, number of interactions with the programme, active weeks in the programme), smoking cessation efficacy (7 and 30 non-smoking days reported by the patient) and safety (adverse events spontaneously reported

and actively investigated by questionnaire, after completion of the 8-week programme). Data were statistically analysed; in addition, post hoc analyses were carried out, given the non-normal distribution of the most predictive variables or dichotomous outcome variables. Overall, the study produced encouraging engagement data: on average, each participant opened the app more than 100 times during the 8 weeks of the study (mean = 110.6, median = 69); participants had numerous interactions with the programme (mean = 214.4, median = 178) and remained engaged for a mean of 5.3 weeks (median = 5 weeks). In addition, at the end of 8 weeks, 45.2% of the intention-to-treat sample reported 7 non-smoking days and 26.2% reported 30 smoke-free days. The few adverse events reported were consistent with nicotine suspension symptoms, while no safety events occurred that were specifically attributable to the product.

Figure 1 - Patient disposition for study NCT02656745, on the product Clickotine

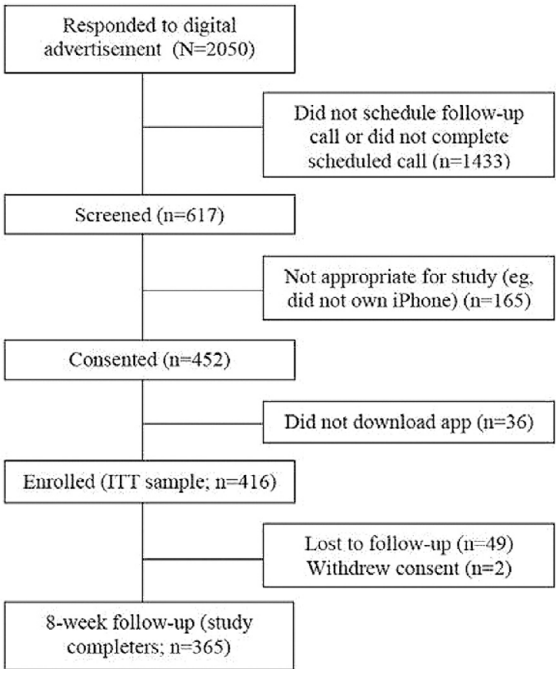


Figure 1 shows the study flowchart (see *clinicaltrials.gov*: NCT02656745).

3.2. Intervention for anxiety management (Unwinding Anxiety)

This is an illustrative case of a RCT in comparison with habitual therapy, carried out on a sample of about 60 subjects (a common number in pilot studies), with evaluation of outcomes both for engagement/acceptability and for efficacy.

Unwinding Anxiety is a behavioural intervention programme, usable on a smartphone or tablet, to help the patient manage anxiety, including generalized anxiety disorder, panic attacks and social anxiety. The programme includes video lessons, exercises, weekly contact with experts, diary entries (journaling), participation in a community moderated by experts, and various daily assessments.

Pilot testing of Unwinding Anxiety comprised a RCT against habitual therapy alone, in subjects with generalized anxiety disorder, to evaluate their engagement and the programme's acceptability, measure its effects in association with habitual treatment versus habitual treatment alone, and carry out preliminary evaluation of the mechanism of action. The study involved 65 adult patients (of whom 57 proved eligible for evaluation). Inclusion criteria included possession of a smartphone and a GAD-7 (General Anxiety Disorder-7) score of 10 or higher.

Primary outcome measures were the number of modules completed (to evaluate engagement) and changes in Penn State Worry Questionnaire score (PSWQ). Other outcome measures included use of validated questionnaires for evaluation of mindfulness, interoception, anxiety level (GAD-7) and acceptability of the programme for users (Net Promoter Score - NPS). The investigators intend to use the results of this phase to design a broader phase 2 study. (See *clinicaltrials.gov*: NCT03683472).

It is interesting to note that, in an independent study by Australian investigators, Unwinding Anxiety proved to be one of the only two apps (out of 348 health and wellness apps assessed) to obtain a score of 4/5 (the highest score obtained). The study looked at multiple parameters in terms of the programme's operation and its potential to modify behaviour[76].

In addition, a recent pilot study investigated the effects of Unwinding Anxiety in a sample of United States doctors with anxiety (n = 34), demonstrating 48% reduction of anxiety (GAD-7) after 28 modules (1 month), and 57% reduction after 3 months ($p < 0.001$ in both cases)[77].

4. Characteristics of pivotal studies

A pivotal study is study specifically designed to enhance data collected during development, and thus provide adequate clinical evidence of efficacy and safety for evaluation by a regulatory agency. In all cases in which evidence in the literature is insufficient for purposes of CE certification, the manufacturer must carry out a pivotal study.

Generally, proof of efficacy for DTx should come from high-quality clinical trials, robust and compliant with state-of-the-art methodological standards for evidence based medicine. A useful reference is the extension of Consolidated Standards of Reporting Trials (CONSORT) to include web-based and m-health interventions[78]. In addition, it should be

demonstrated that the study tested the software for all foreseen uses and user groups, respecting the target population, conditions of use and usage environment.

Study design must enable collection of statistically significant evidence, involving sufficiently large samples, whose size must be defined beforehand on the basis of a statistical hypothesis. Study design must also enable documentation of the device's possible place in therapy, defining the appropriate control group accordingly. Since the characteristics of medical software often make blinded study design very complicated, choice of endpoints and metrics is essential to a study's reliability and methodological consistency.

Multicentre studies are recommended, particularly for pivotal studies. In addition to enabling collection of data from a number of hospitals/geographical areas, and thus offering evidence that is more representative of the potential target for DTx, this approach should also offer the advantage of reducing the lead time for recruitment - a particularly important consideration with an eye to the risk of the proposed technology becoming outdated.

In Europe, valuable information for investigators can be found in the NICE "Evidence standards for digital health technologies"[79], issued in March 2019 by the National Institute for Health and Care Excellence, UK.

Clinical evidence requirements set out by NICE vary according to the type of intervention the device carries out, according to whether its aim is preventive or therapeutic. In the latter case, requirements are understandably more stringent.

Software is classified along the lines presented in the NICE guidance, which places DTx evidence requirements within tier 3, subdivided in turn into tiers 3a and 3b on the following basis:

- If the software is intended to modify the subject's behaviour, being used for preventive behaviour change or to allow self-management of a diagnosed condition, tier 3a evidence standards apply;
- If the software is used for treatment, being designed to provide or guide treatment, active monitoring and clinical calculations, or to provide or guide a diagnosis, tier 3b evidence standards apply.

The standards are cumulative. This means that, while each tier comprises specific evidence of effectiveness requirements (see *Tables 3* and *4*), it also requires full compliance with the evidence standards of lower tiers. Thus, tier 3 DTx must also meet the tier 1 and 2 standards.

Table 3 - NICE evidence for effectiveness standards for tier 3a devices

Category	Minimum evidence standard	Best practice standard
Demonstrating effectiveness	High quality observational or quasi-experimental studies demonstrating relevant outcomes. These studies should present comparative data. Comparisons could include: • relevant outcomes in a control group • use of historical controls • routinely collected data. Relevant outcomes may include: • behavioural or condition-related user outcomes such as reduction in smoking or improvement in condition management • evidence of positive behaviour change • user satisfaction.	High quality intervention study (quasi-experimental or experimental design) which incorporates a comparison group, showing improvements in relevant outcomes, such as: • patient-reported outcomes (preferably using validated tools), including symptom severity or quality of life • other clinical measures of disease severity or disability • healthy behaviours • physiological measures • user satisfaction and engagement • health and social care resource use, such as admissions or appointments. The comparator should be a care option that is reflective of standard care in the current care pathway, such as a commonly used active intervention.
Use of appropriate behaviour change techniques (if relevant)	Be able to show that the techniques used in the DHT are: consistent with recognized • behaviour change theory and recommended practice (aligned to guidance from NICE or relevant professional organisations) • appropriate for the target population.	Published qualitative or quantitative evidence showing that the techniques used in the DHT are: • based on published and recognized effective behaviour change techniques • aligned with recommended practice • appropriate for the target population.

Table 4 - NICE evidence for effectiveness standards for tier 3b devices

Category	Minimum evidence standard	Best practice standard
Demonstrating effectiveness	High quality intervention study (experimental or quasi-experimental design) showing improvements in relevant outcomes, such as: • diagnostic accuracy • patient-reported outcomes (preferably using validated tools) including symptom severity or quality of life • other clinical measures of disease severity or disability • healthy behaviours • physiological measures • user satisfaction and engagement. The comparator should be a care option that is reflective of the current care pathway.	High quality RCT in a setting relevant to the target country's health and social care system, comparing the DTx with a relevant comparator and demonstrating consistent benefit, including in clinical outcomes in the target population, using validated condition-specific outcome measures. Alternatively, a well-conducted meta-analysis of RCT if there are enough available studies on the device under investigation.

Hence the importance of analysing requirements for prevention devices. The NICE evidence standards include minimum and recommended levels of scientific evidence, the latter being defined as "best practices".

It can be seen that studies on products in advanced phase development (*Table 1*) all fall within the tier 3b evidence for effectiveness standards, while pilot studies can have greater flexibility in design. Three illustrative cases of pivotal studies on DTx in advanced phase development are presented below. All three studies showed statistically significant benefit for DTx (versus the control treatment) in terms of primary endpoints, in many cases related to clinical efficacy or to prevention of the disease concerned. It should be borne in mind that both therapeutic and preventive aims are consistent with common definitions of DTx - e.g., that of the Digital Medicine Society/Digital Therapeutic Alliance.

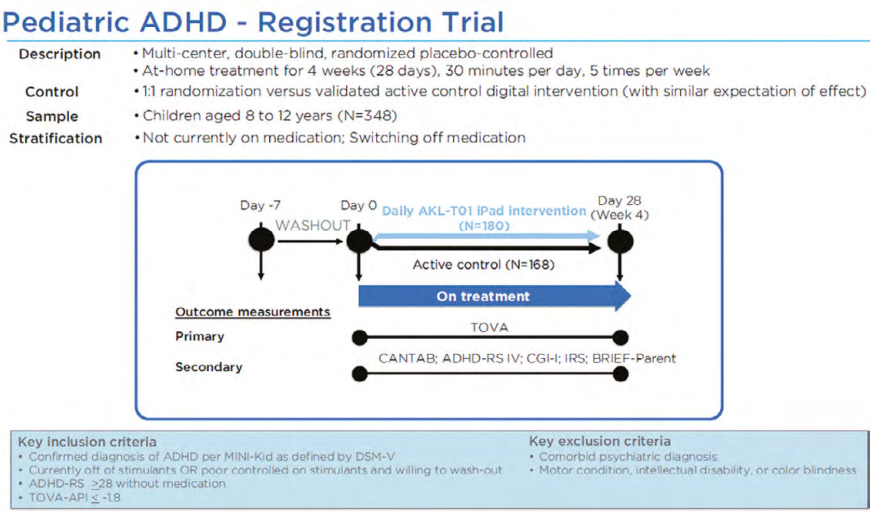
4.1. DTx for paediatric attention deficit hyperactivity disorder (ADHD) (Akili, AKL-T01)

This is an illustrative case of a pivotal study for DTx used in monotherapy, controlled versus active digital intervention.

AKL-T01 is a digital treatment based on a video game interface, developed for treatment of paediatric ADHD. The software sends motor and sensory stimuli, able to reach and activate the prefrontal cortex (the brain area involved in cognitive functions). Clinical development comprised a number of studies, up to completion of a multicentre pivotal study (20 centres) that was randomized, double-blind and controlled versus active intervention. The study involved 348 children of 8-12 years with confirmed diagnosis of ADHD. DTx was used in monotherapy (the children were not taking pharmacological treatment, or were able to suspend any prior pharmacological treatment), the control intervention being a different videogame (AKL-T09); the primary endpoint was improvement of the Test of Variable Attention Performance Index, measured basally and then at the end of 4 weeks (therapy about 25 minutes per day, 5 days per week)[5].

This study is important, as one of the first and most rigorous investigations of DTx in a large prospective RCT, with an approach similar to that usually used for pharmacological treatment. *Figure 2* shows the study design flowchart (see the site *clinicaltrials.gov*: NCT02674633).

Figure 2 - Flowchart of study NCT02674633, to evalutate the effects of the product AKL-T01 for treatment of ADHD in children



4.2. DTx for treatment of substance abuse (reSET)

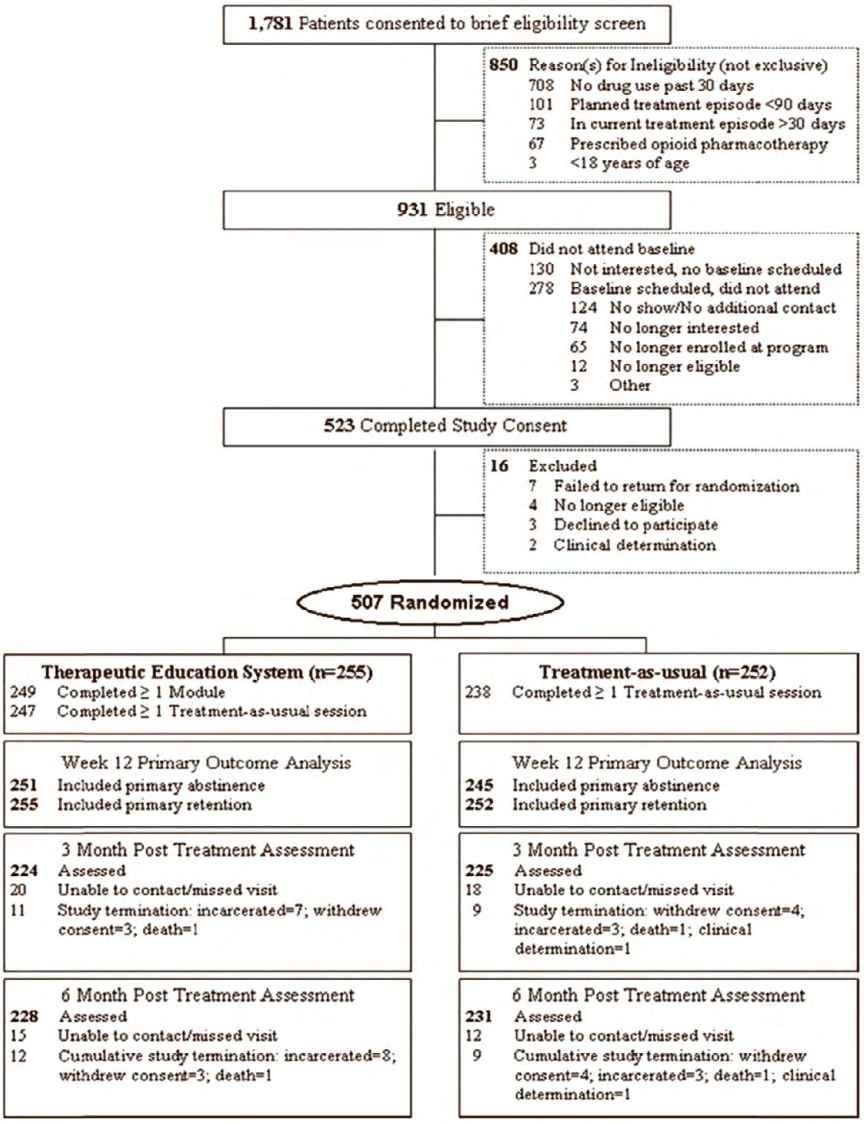
This is an illustrative case of a pivotal study for DTx used in association with a modified habitual therapy, the control being the habitual therapy alone.

reSet is a digital intervention for treatment of substance abuse. It is a 90-day cognitive behavioural therapy CBT, to be administered as a partial replacement of habitual therapy (part of which is substituted with reSet), and is complementary to normal contingency management. This solution enables integration of a dashboard for doctors and other healthcare operators, with information on the patients' use of reSet, substance use (both as reported by the patient and based on laboratory data), and other information provided by patients.

The pivotal, randomized, controlled multicentre study (10 centres) initially involved 1,781 adult subjects, 507 of whom were randomized to receive only habitual therapy or reSet in combination with a programme of modified (reduced) habitual therapy. The reSet component could be run by the participants on computers at the study centre, or managed autonomously by them outside the centre. Preset primary outcomes were abstinence from heavy drugs or alcohol in the last 4 weeks (self-reported or based on urine analysis)[3].

The study showed that likelihood of abstinence increased in a statistically significant manner for subjects using stimulants. In particular, patients treated with reSet showed a lower dropout rate from treatment than

Figure 3 - Patient disposition in study NCT01104805, on the product reSet



in the case of habitual treatment (Hazard Ratio = 0.72 [IC 95% CI, 0.57-0.92], p = 0.010), as well as an increase in the period of abstinence (Odds Ratio = 1.62 [IC 95%: 1.12-2.35], p = 0.010); the effect was more marked in patients who, at the time of pre-recruitment screening, tested positive for substances in a urine sample and/or for alcohol in a breathalyser (n = 228) (Odds Ratio = 2.18 [IC 95%: 1.30-3.68], p = 0.003).

Figure 3 shows the flow chart for study enrolment and design (see clinicaltrials.gov: NCT01104805).

4.3. Digital intervention for diabetes prevention (Noom Coach app)

This is an illustrative case of a RCT for a digital coaching programme with a preventive aim.

Noom Coach app is a virtual coaching intervention delivering a diabetes prevention programme through an interactive interface. The app includes messenger functions between coach and participants, group messages, support to behavioural changes by setting of daily challenges, educational articles on DPP, input on food intake and automatic feedback on dietary choices. After an extensive pilot phase, a RCT was recently completed with 202 adult participants, the primary aim of which was to evaluate the efficacy of the mobile platform Noom Coach DPP by comparison with a habitual medical intervention (participants were free to seek assistance or medical support during the study, and were also given a hard copy version of the DPP)[6]. The primary endpoint was modification of body weight as measured basally, at 6 months and at the end of the study (total duration, 52 weeks); further objectives included variations in glycosylated haemoglobin levels, in productivity at work (by validated questionnaire), and in quality of life (by questionnaire CDC HRQOL-4).

5. Evaluation of the safety profile

Alongside evaluation of benefit, pivotal studies (or RCT) generally provide information about possible side effects associated with the (new) treatment under evaluation. This measure, together with evaluation of benefits, serves to determine tolerability and thus to evaluate the risk-benefit ratio of the new treatment.

DTx interventions can have undesired effects. While these are generally

less serious than those caused by traditional drugs, and often more readily managed, they may be more frequent than in the control arms of the studies concerned and must, in any case, not be underestimated.

For example, a study that demonstrated the efficacy of DTx for smoking cessation showed side effects in two patients (mood swings, nightmares), probably associated with the treatment, and, in a few other cases, fatigue (not associated with the treatment)[7].

Recently, in illustrating the benefits of Endeavor (previously known by the experimental code AKL-T01), a video game-based DTx treatment of paediatric ADHD that received FDA market approval in June 2020, the treatment was not associated with any severe adverse events. However, in 9.3% of cases, patients treated showed non-severe adverse events associated with the treatment, including a sense of frustration, headache, vertigo, emotional reactions, nausea or aggressiveness[80].

Adverse events that can be associated with DTx must in any case be measured and evaluated. Not in every case, however, are events attributable to the DTx intervention. For example, in a RCT to measure the efficacy of a DTx intervention in management of diabetes, there was a low percentage of hypoglycaemic events, hospital admissions and visits to A&E, the rates being wholly comparable to those in the control group), and these adverse events were not related to the study treatment[8].

As in the case of traditional therapies, careful evaluation of undesired effects that can be associated with DTx is possible thanks to post-marketing studies (phase IV studies). This makes it possible to obtain information on broader and more heterogeneous populations, as well as on long-term safety.

An equally interesting, and perhaps more important, topic is that of dropouts - in other words, those who discontinue the DTx before the end of the trial. In a study to evaluate the efficacy of DTx for treatment of chronic back pain, there was progressive dropout: after 8 weeks of DTx, only 32% of the initial study sample were still following the treatment, while at the end of the study (12 weeks) only 18% were left.

Close attention to DTx design, greater involvement of patients in the development phase and closer attention to user feedback, together with greater user engagement thanks to memoranda, emails, SMS and messages, are aspects that should be focused on with a view to reducing the dropout rate as far as possible.

6. The role of Institutional Review Boards

To favour a system enabling a significant european contribution to the development of DTx, the IRB must have adequate know-how and specific guidelines, bearing in mind that investigation of DTx can differ significantly from that of a drug or of a traditional medical device (e.g., a joint prosthesis), which boards will be more familar with.

DTx study design must guarantee protection of sensitive data and allow management of the rapid technological evolution to which these systems are subject.

In this respect, the main critical issues are controlling changes to the product during the study, and data backups for the study. Given the rapid evolution of stand-alone medical device software, there is every likelihood of frequent version updates for the device during the study.

The manufacturer must therefore factor into the study protocol and the product itself a change control procedure not requiring the approval of an IRB or other authority. This will cover updates such as bugfixes, modifications related to usability criteria rather than to clinical aspects, or other changes of a technical nature that the DTx manufacturer is bound to accept as a matter of course (e.g., updates of an Android iOS platform or health app).

7. Post-marketing surveillance

From the very first issue of a CE certificate, the DTx manufacturer must plan collection of post-marketing clinical data. By definition, the studies concerned must be carried out in compliance with indications for use, in a patient population for which the device is already certified: this means that the studies cannot be used to test new clinical applications of the software, the aim being to confirm the risk-benefit ratio and collect information on large-scale use. In this perspective, post-marketing surveillance studies provide an excellent opportunity to collect important information in terms of treatment compliance and user experience.

The MDR encourages use of follow-up study results to provide new information with a view to enhancing and updating software. Hence the relevance of, for example, adequately controlled post-marketing studies to increase the training database for an artificial intelligence system used in healthcare.

The very nature of DTx enables massive post-marketing data collec-

tion. Manufacturers should therefore set up systems for real-world clinical data collection, while obviously respecting patients' data protection.

An excellent example of this practice is Natural Cycles, a DTx application for birth control. Use of this device has enabled data collection in a number of observational and retrospective clinical studies to evaluate its efficacy, both in experimental use and in real-world settings[24, 81-83]. In addition, the data thus obtained have enabled the manufacturer to identify further indications not strictly linked to demonstration of the device's efficacy, but related to its use, thus making it possible to share important scientific information[84, 85].

The manufacturer's data collection system should also take into account effects on the patient's health once the treatment has stopped.

8. Maximum acceptable modifications to DTx not requiring a completely new start to clinical validation

As already pointed out, by comparison with other forms of drug or medical devices, a peculiar feature of products like DTx is the possibility of rapid technological evolution taking place during the clinical validation phase. This is a particularly sensitive topic, for which clear and well-defined guidelines would be appropriate.

In this respect, attention should be drawn to the interesting proposals drawn up by Torous et al. in their paper "Towards a consensus around standards for smartphone apps and digital mental health"[86]. Stating that they *"represent leaders in mHealth research, industry and health care systems from around the globe"*, the authors state:

"Changes in technology may mean that app updates need to be re-evaluated for their efficacy. Small cosmetic changes, platform changes and aspect changes do not likely require a retest of an intervention, as long as the therapeutic principle that has been evaluated remains intact. […] However, significant changes, such as adding a new therapeutic principle or substantial changes to that principle, must demonstrate efficacy through the same evaluation pathways as novel therapeutics.

Our recommendations are:

a. *newly adapted therapeutic principles, which should be identified and defined, must undergo controlled clinical trials to determine their efficacy and effectiveness;*

b. *small changes to an app with an evidence base need not undergo another clinical trial, but any major change requires a re-evaluation of app effectiveness."*

On the basis of these general principles, it is fundamental to understand how to distinguish the "significant" or "small" modifications on the basis of which the product's effects may or may not have to be re-evaluated.

The manufacturer must first define policies to include a definition of how any modifications can impact the device, on the basis of a risk analysis. The following is an example readily applicable to DTx:

a. Major modification

- any variation that can potentially have an impact in terms of safety, efficacy and risk characteristics of the software system - e.g., creation of a new training database with different clinical indicators;
- any variation in intended use, for example:
  - use of the system for a different patient population
  - integration of the system with a module to enable flagging of a clinical emergency
  - integration of the system with a module to manage interaction with wearable devices
  - change to the method of interaction with the patient, introducing vocal interaction
  - integration of the system with a new, additional parameter that can be measured to provide input for the algorithm
  - any change in the main architectural structure, meaning a change to the organization of modules and software elements that will in turn bring changes to the data flow for the intended clinical use, or to segmentation (e.g., transition from a system based on a locally used downloadable app to a mainly cloud-based system)
  - any change that could cause incompatibility between the modules or with the interface systems (database or operating system);

b. Minor modification

- any modification not included in the definition of "major", such as:
  - improvement of performance, without modification to intended use or new input types
  - update of training or validation database, with data that are comparable in terms of quality and information content to those used in the previous version;
- modifications of access, logistic or management input, without changing intended use, such as:

- new means of user identification (e.g., biometrics rather than password)
- data input by professional user's voice command;
- update of user interface, new icons
- translations
- update of user manual
- modifications or integrations to non-critical software of unknown provenance (SOUP)
- bots for technical assistance to patients/professional users - e.g., for password change assistance.

Each modification classified in this way has to be interpreted and analysed when proposed within a clinical study:

- in the case of a major modification, it should be evaluated in detail, to identify whether the modification is completely unacceptable or the information collected with the product in the previous version is still partly significant;
- minor modifications, which we have seen should be acceptable and not involve the need for introducing a completely new validation process, can be communicated to investigators and formalized by updates to the Investigator's Brochure; where appropriate, they can also be communicated to users (e.g., in the event of minor modifications to the interface, in which case training activities could possibly be indicated with a view to guaranteeing that the user is able to continue using the product);
- bugfixes are to be considered acceptable, and should be communicated to investigators and users with automatic notifications (e.g., in-app notifications).

What is known

- Software delivering digital therapeutics (DTx) consists of medical devices and, in Europe, must therefore comply with Regulation (EU) 2017 745
- The Regulation states that it is necessary to demonstrate clinical benefit, by means of clinical investigation, but it does not provide details regarding the characteristics of such investigation
- Today, there are examples of approved DTx, while many others are in the development phase. The level of evidence available, or that is being generated, varies
- Evaluation of clinical benefit for DTx must be based on demonstrable and statistically significant clinical evidence regarding improvement

of a specific, measurable health parameter. The novelty and innovativeness of these technologies must not be considered ends in themselves, because not everything that is technologically advanced is automatically useful, efficacious and cost-effective, to the same extent as (if not more than) traditional methods
- Traditional evidence-based research methods are not always bound to be perfect or automatically applicable to DTx, but there must be a clear aim to achieve exhaustive description of the risk-benefit ratio and to develop a good knowledge of what can be reasonably foreseen in terms of clinical use.

What is uncertain
- In the absence of precise recommendations in the Regulation, it is not clear what must be the characteristics of clinical trials to support DTx certification in Europe
- DTx present peculiar characteristics that raise specific needs to be addressed during study design, with a view to obtaining exhaustive characterization of the risk-benefit profile: choice of control, as well as metrics for outcome measurent in relation to efficacy and safety, must often be customized on a case-by-case basis.

What we recommend
- More detailed regulations are needed in Europe regarding clinical investigation of DTx, in order to ensure adequate and uniform standards of efficacy and safety for DTx medical devices
- To enable developers to collect clear evidence of benefit, and to enable its correct evaluation by regulatory authorities, the following recommendations are made:
  - possibility of expressing clinical benefits through metrics appropriate not only to the intended use, but also to the technology involved
  - in a controlled study, not only a clinical but also a technical rationale for choice of control (e.g., in the case of DTx for cognitive behavioural therapy, the control could be a drug or CBT administered in person, in a telemedicine setting or by means of a normal videogame)
  - in the clinical protocol, possibility of defining the pipeline of possible foreseen changes to technical, interface and software architecture, defining for each of them an impact policy in relation to the conduct of the study

- adequate patient enrolment numbers, with a view to demonstrating the possible advantages of DTx by comparison with the control arm
- activation of patient engagement strategies to optimize planning and conduct of the study (e.g., limiting the possible dropout rate), interalia with a view to enhancing alignment of study aims with fulfilment of patients' needs
- clinical validation plans, taking into account long-term side-effects

- It is also recommended that clinical trials of DTx can be evaluated with the involvement of different regulatory authorities - e.g., the European Medicines Agency for studies comparing DTx with a drug, or in cases where its intended use is similar or identical to that of a drug.

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Access/reimbursement policies for digital therapeutics already in use in national health systems

The development of a business model and access policy for digital therapeutics (DTx) is becoming a recognized need and a matter of discussion in many countries, which can benefit from examples already in place in other systems. Until recently (last update of this article: April 2021), forms of reimbursement policy for digital health solutions, including DTx, were mostly lacking in many parts of the world; this scenario is nevertheless quickly changing, having received considerable impetus from recent developments in a number of countries. Of particular interest in Europe is the recent approval of the Digital Healthcare Act (DVG, Digitale-Versorgung-Gesetz) in Germany, introducing the possibility of an accelerated pathway to the market for DTx. Taking such developments into account, the aim of this paper is to present a brief overview of the most representative features internationally, with the focus on a number of key countries.

In the **USA**, the lack of free medical care for all means that the onus for payment of digital healthcare solutions is to a very large extent borne directly by users/patients. This creates a patchwork scenario, with examples of digital health or DTx solutions paid directly by users, alongside growing numbers of cases where the costs are covered by a number of different players. Some digital health solutions have acquired great popularity - e.g., OneDrop (diabetes management), Headspace and Calm (mental health/meditation); such products attract millions of paying users, normally with a monthly subscription fee credited directly to the developers. In addition, private health insurance schemes and a number of hospitals are starting to develop or to license out their own digital health solutions, in order to reduce the typical user's risk profile (in the case of insurance companies), or to provide more adequately for the population's specific health needs in

the catchment areas concerned, while also (in the case of hospitals) promoting achievement of federal targets for reduction of hospital admissions. Another emerging form of reimbursement in the United States is the inclusion of digital health solutions in the healthcare packages of large corporations, which subsidize treatment costs by including these solutions in corporate employee benefit packages.

Promoting access to digital health approaches and tools is an important objective in the USA's mid-term planning, a case in point being the inclusion of DTx in the 2020-2025 Federal Health IT Strategic Plan of the Office of the National Coordinator for Health Information Technology. Among the strategies identified, the plan aims to develop evidence-based use of DTx as a treatment option for prevention, management and treatment, by use of smartphones, tablets and other personal devices.

In addition, as a result of the current CoViD-19 pandemic the FDA has further stepped up its active support for the approval of prescription DTx. Evolving the pre-existing "Pre-Cert" programme, designed to regulate and accelerate the development of software as medical devices (SaMD), the FDA issued guidance documents introducing appropriate degrees of flexibility on a large number of regulatory requirements, including a temporary waiver of premarket notification requirements under section 510(k) of the Food, Drug, and Cosmetic Act. In January 2021, these relaxations of previous regulatory requirements were made permanent for 91 devices and SaMD tools, out of the 221 Class I and Class II medical device types covered by the waiver categories. Details of the updated waiver status for the classes concerned are available at:

https://www.federalregister.gov/documents/2021/01/15/2021-00787/making-permanent-regulatory-flexibilities-provided-during-the-CoViD-19-public-health-emergency-by#p-64 (last accessed March 29, 2021).

In the **United Kingdom**, the National Health System (NHS) has for some time offered a broad catalogue of digital solutions dedicated to health and wellbeing; these are certified and accessible via the NHS app library, which is in turn part of the NHS app. In some cases, the NHS has negotiated licensing agreements with digital health app developers, in order to make these solutions available free of charge to all patients. The apps falling under this heading are mostly intended to support the user/patient in playing a more active role towards the management of their mental and physical health. To be included in this catalogue, products

have to demonstrate compliance with the standards defined by NHS Digital, including the need for evidence of clinical outcomes achieved or reported by patients, clinical safety and technical stability; information is also required on data protection, usability, acceptability and interoperability. Details of assessment criteria used by the NHS for health apps, and related digital tools, can be found via the following link:

https://www.nhsx.nhs.uk/key-tools-and-info/digital-technology-assessment-criteria-dtac/ (last accessed March 29, 2021).

The NHS roadmap for patient digital services is broad, diversified and still evolving. The "Empower the Person Roadmap", which is periodically updated, provides information on the status of resources (available, recently introduced, under development, expected). The complete roadmap, now in its fifth version, is available at:

https://eu-rm.roadmunk.com/publish/0dbd8ebaa98e26573e09b1d-1fc74433d486ee5d2/ (last accessed March 29, 2021).

It is also interesting to note that the NHS has complemented this promotion of digital services by setting up the NHS Digital Academy. A joint venture between the NHS, Imperial College London, the University of Edinburgh and Harvard Medical School, the Digital Academy aims to promote training and development for a new generation of digital leaders, able to guide the transformation of the NHS.

At **European level**, in April 2019 the European Commission (EC) published its "Proposed Guiding Principles for Reimbursement of Digital Health Products and Solutions" as one of four working papers developed collaboratively by members of the eHealth Stakeholder Group (eHSG), the EC's expert group on European digital health policy. The paper contains recommendations that address the peculiar nature of digital health solutions and their difficulty in entering funding and reimbursement pathways in Europe, namely:

- specific criteria are needed to make appropriate reimbursement decisions for digital health products and solutions;
- relevant digital health products and solutions should benefit from either EU or national funds within innovation investment funds;
- European guidelines for relevant and fit-for-purpose evidence generation for digital health products and solutions should be developed;
- the specifics of digital health products and solutions must be considered when developing instruments for assessing and rewarding the value they pro-

vide for patients, healthcare actors, health systems' sustainability and society.

The paper can be downloaded at: https://www.medtecheurope.org/wp-content/uploads/2019/04/30042019_eHSGSubGroupReimbursement.pdf (last accessed April 7, 2021).

In **France**, a significant example of reimbursement for a digital health platform is that of Diabeo (Voluntis), a digital medical device for insulin dosage. The HAS (Haute Autorité de Santé) has approved reimbursement of Diabeo, solely for cases in which it is prescribed in the context of a telemedical consultation; the background to this decision is the 2019 authorization for doctors in France to offer teleconsultation, via approved telemedicine platforms, as a recognized activity for which they are paid.

The case of Diabeo in France can obviously create a precedent that can facilitate and speed up comparable approval measures for reimbursement of other digital health solutions, including DTx. It is reasonable to think that the dynamics of access to reimbursement in a teleconsultation setting will bring forward the development of further solutions by providers interested in accessing the French market (or that this precedent will provide a rationale for developing digital health or DTx with a view to their being prescribable and usable on a teleconsultation basis).

A further example also deserves mention in France: the HAS has included in its reimbursable list for health products and services Moovcare Poumon, a medical device based on software for telemonitoring of relapses and complications during follow-up of lung cancer patients at high risk of relapse. The original document containing the HAS approval can be accessed via the following links:

https://www.has-sante.fr/jcms/c_2964253/fr/moovcare-poumon

https://www.has-sante.fr/upload/docs/evamed/CNEDIMTS-5682_MOOVCARE%20POUMON_09_avril_2019_(5682)_avis_occultation.pdf

(last accessed March 29, 2021).

In **Belgium**, at the initiative of the federal government in collaboration with multiple stakeholders, the mHealthBelgium platform is available for mobile applications with CE marking as medical devices. This platform centralizes all relevant, necessary and valid data for any such applications to be used by patients, healthcare professionals and healthcare institutions.

The platform (accessible in Dutch, French and English) provides information on CE marking, the GDPR, conformity, compliance with safety and

authentication rules, as well as the cost and financing of the app concerned.

Apps on the platform are classified on the basis of a 3-tier validation pyramid:

- M1, the basic level, includes criteria such as CE certification as a medical device and GDPR compliance;
- M2 is based on criteria regarding interoperability and connectivity to the eHealth platform;
- M3 is for apps that can demonstrate added value in socio-economic terms and are eligible for reimbursement.

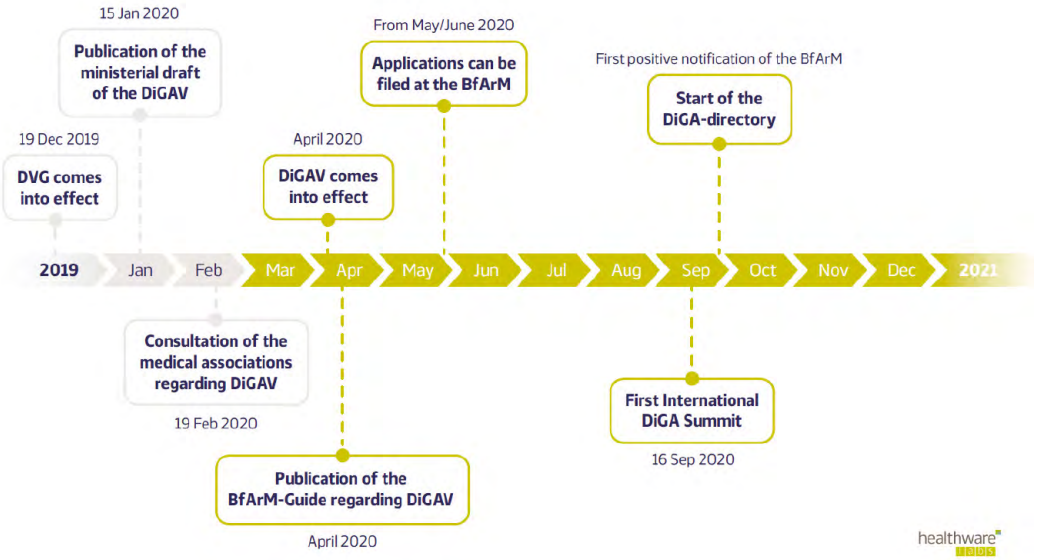
Overall management of mHealthBelgium is carried out by beMedTech (the medical technology industry federation) and Agoria (the association representing companies in the technological sector), in close collaboration with three national authorities:

- the Federal Agency for Medicine and Health Products (FAMHP), as the authority responsible for safety, quality and efficacy of drugs and health products, which is responsible for tier M1;
- the eHealth platform, as the federal eHealth organization implementing the infrastructure for exchange of information in the health sector, which is responsible for tier M2;
- NIHDI, the National Institute for Health Insurance and Invalidity, responsible for reimbursement of health products and services, which is responsible for tier M3.

Further details can be found at the following site:
https://mhealthbelgium.be (last accessed March 29, 2021).

The most relevant development in Europe is the approval by the German Parliament of the new rules supporting digital innovation in **Germany**. The new roadmap dates from December 2019, with the introduction of the DVG (Digitale-Versorgung-Gesetz), a specific regulatory framework for digital health applications (DiGA, Digitale Gesundheitsanwendungen), which entered into force on 21 April 2020. The Federal Ministry of Health order setting out implementation of the DVG can be consulted online (https://hih-2025.de/wp-content/uploads/2020/04/DiGAV_RefE.pdf; last access March 29, 2021). On 27 May 2020, the BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte) started to receive the first applications; the starting date for the register, with the inclusion of the first DiGA, was scheduled for October 2020 *(Figure 1)*. It was announced recently that the DVG will be iterative in nature: consistent with agile

Figure 1 - Steps in the implementation of the fast-track procedure in Germany



www.bfarm.de/diga_en, modified

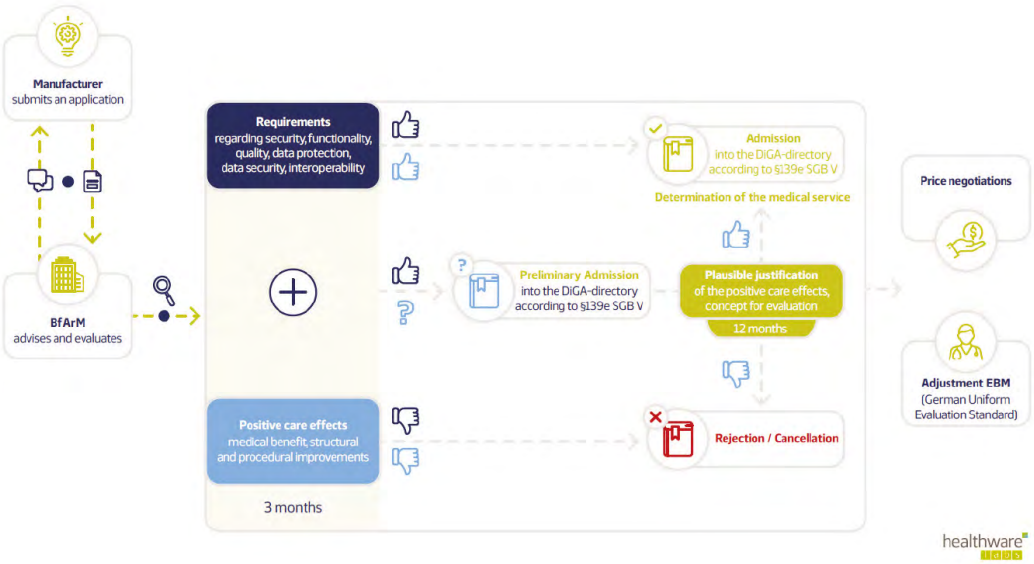
development processes, the regulations will follow a sequence of learning and adaptation over a period of time.

The new German regulations, potentially impacting 73 million citizens covered by the national health service and their GPs, aims as a whole to harmonize developers' needs (rapid placement on the market and minimization of obsolescence risk) and the regulatory requirements for medical devices, in relation to the need for scientific validation before placement on the market.

The cornerstone of the regulations is the setting up of a fast-track approval process for digital health solutions (see *Figure 2*).

As of May 2020, less than a year after the first draft of the DVG was drawn up, health app suppliers started to make fast-track application to the German regulatory agency BfArM, supported by documentation of the scientific development process together with technical information on data safety and on the app's operational testing/results. BfArM has issued specific guidelines on fast-track applications, for manufacturers, service suppliers and users. The guidelines are probably the most complete and accessible document regarding the regulations and their application; an English ver-

Figure 2 - Flowchart for fast-track approval of digital applications in the German healthcare system



www.bfarm.de/diga_en, modified

sion, published at the end of August 2020, is available online (https://www.bfarm.de/SharedDocs/Downloads/EN/MedicalDevices/DiGA_Guide.pdf?__blob=publicationFile&v=2; last accessed March 29, 2021).

On 16 September 2020, the first International DiGA Summit took place. Examining the regulatory state of the art, the event was attended by over 1,500 participants from more than 40 countries, with contributions from BfArM and the Federal Ministry of Health.

At the present date (April 2021), twelve DiGA are included in the DiGA directory (https://diga.bfarm.de/de; last accessed April 9, 2021).

The main points in the current German scenario can be summed up as follows:

- DiGA are defined as CE marked medical devices with a low risk classification (classes 1 and 2a), whose main function is based on digital technologies. Designed for health treatment or as a support for identification, monitoring, treatment or mitigation of a disease or disability, they can be used by the patient independently, or with the help of a healthcare professional;
- DiGA can be prescribed and reimbursed only after approval by the BfArM and inclusion in the DiGA register;

• The DiGA must have demonstrated one or more positive effects on health. These effects can comprise a medical benefit, or a relevant improvement for the patient in terms of treatment content and processes. Examples of the latter category include patient compliance, autonomy and health literacy, together with facilitation of healthcare access and further outcomes related to improvement of the patient's everyday life;

• Studies to generate evidence of benefit must be carried out in Germany. In specific cases, studies carried out wholly or in part in other countries can be accepted, on condition that healthcare status and the study population are similar to those in Germany;

• The supplier can apply for definitive or provisional registration. In the event of provisional registration, a test period of up to 12 months is granted; it should be borne in mind that the supplier can apply only once for provisional registration. If an application for definitive registration is rejected, the supplier can no longer obtain provisional registration, but must wait a year before presenting a new application (obviously supported by further data and evidence, in addition to those presented at the time of the first application). The supplier must therefore carefully weigh up the pros and cons of applying for definitive or provisional approval, on the basis of already available and pending evidence. The BfArM provides informal consultancy on these matters;

• DiGA suppliers can demonstrate the efficacy of their solutions on the market within one year, and negotiate prices with the umbrella organization for public health insurance cover in Germany (GKV-SV, Gesetzlichen Krankenversicherung Spitzenverband);

• Doctors are authorized to prescribe health apps that have passed the required data safety and operational tests, and have been placed on the BfArM register *(Figure 3)*.

• Telematic consultations are becoming the norm. Healthcare professionals must actively promote telemedicine services to patients, for example on their websites. Prices for telecare services are still under negotiation, but should soon be defined;

• German public healthcare insurance bodies must send details of patient demographics and health status in anonymous form to a central databank managed by the German government. Research organizations and universities can request access to data for research purposes. This will guarantee better access to patients' data for research;

Figure 3 - Prescription and reimbursement procedures for digital health applications in Germany

https://hih-2025.de/wp-content/uploads/2020/03/2020-03-06-hih_FastTrack_english-magazin-version.pdf, modified

• Every insured person will have access to an electronic medical file. By January 2021, this access must be available to every person covered by a public health insurance scheme (73 million people);

• Doctor-patient communication and prescriptions, initially in hard copy, will gradually be migrated to electronic channels. Electronic prescriptions for medicines, treatment and laboratory/instrumental examination, specific indications by the doctor and certificates of invalidity for employers will be allowed. Traditional communication by fax will not be encouraged;

• Pharmacies, healthcare professionals and hospitals will be required to use secure data networks. All pharmacies, hospitals and healthcare professionals must connect to the German network for secure health data, made available by Gematik. In the event of non-compliance, they will be liable to fines;

• Health insurance bodies will make online enrolment available to those covered;

• This innovation of health services will be subsidized: the German government has made annual funding of €200 million available for another four years, in support of innovative projects in the health sector.

Illustrative cases of reimbursement policy for digital health or DTx

Globally, an increasing number of digital health or DTx products are being considered for coverage by local, regional or national payers. The CoViD-19 pandemic has in fact exposed the challenges payors face in delivering accessible high-quality care outside of traditional office-based visits. Payors are now considering additional options for how to best meet patient needs and close gaps in care with non-traditional approaches. While the list of reimbursed products is evolving, some "historical" examples still provide reference cases.

A significant example of accessibility, involving **the UK and US markets**, is that of Sleepio, a customized DTx product for management of sleep disturbance, which is based on cognitive behavioural therapy (CBT) techniques and has been clinically validated (33 peer-reviewed scientific publications, including eight randomized controlled trials - RCT). On the basis of the clinical evidence obtained, the American College of Physicians has recognized Sleepio as the first line CBT in treatment of chronic insomnia. Thanks to a partnership with the NHS, Sleepio is now freely available in a number of UK regions (including 8 million users in the London metropolitan area and 2.3 million in the Thames Valley). In the US, healthcare benefits management company CVS has included Sleepio in its formulary and over 2 million users are privately covered by employeers that include this app in employee benefit plans; currently, over 12 million people thus have free access to Sleepio.

Conclusions

The DTx industry is still in its infancy and rapidly evolving and, while close attention is rightly given to setting up regulatory and clinical development roadmaps, it is also important to consider that the generation of significant revenue flows is, and will remain, one of the main challenges for this sector on all markets.

Europe is no exception in this respect, having opened the road towards a serviceable access model; the recently introduced German regulations, which mark a definite step forward along this road and can be seen as a strong catalyst, offer a model that other European countries can take inspiration from.

Currently, DTx are not available in Italy, however different players are active in research and development. Moreover, the Italian Medicines Agency (AIFA) has taken the first steps towards regulating DTx in Italy and has made the new objective official in its 2020-2022 Performance Plan, which includes *"Proactively monitoring the digital therapy applications currently in the development, and through interaction with the various stakeholders both at national and European level in the form of targeted meetings and workshops, identifying the aspects that fall within the competence of AIFA, acting as a promoter at European level of the process of adaptation of the regulatory system"*. Further details can be found at: https://performance.gov.it/performance/piani-performance/documento/1332 (last accessed April 13, 2021).

As an Italian Working Group, we are looking with great interest at the evolving scenario in Europe in terms of access and reimbursement policy, and believe there is an urgent need to evaluate and define models that can be practicable and sustainable.

What is known

- In most regions and countries, the lack of adequate reimbursement pathways is among the most important barriers to the digital transformation of health and care. However, actual examples of reimbursement frameworks are increasingly available and some countries already have functioning processes in place. In this overall picture, the CoViD-19 pandemic is acting as a catalyser and it is possible that many contingency measures will become permanent, thus speeding up progress towards access to DTx.

What is uncertain

- One year on from the activation of the DiGA repository in Germany, preliminary and encouraging data on this program are available. A longer period is needed to understand how suppliers are responding, the approval/rejection rate and conversion rate from provisional to permanent approval, the lead time for dealing with applications, etc. The status of these and other indices will shed important light on the practicability and sustainability of this model
- It is not known what the position of the European institutions will be, whether there will be an evolution towards European guidelines, or whether it will be possible for DTx to be centrally approved in the

same way as pharmaceuticals by the EMA. Similarly, the role played by regulatory institutions in the individual countries will have to be clarified (e.g., whether in Italy the role currently played in Germany by the BfArM can / must be fulfilled by the Ministry of Health alone, or in cooperation with AIFA and/or other institutions).

What we recommend

- We recommend considering the German case as a basis for developing models in other European countries and, in particular, for outlining an Italian proposal.

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Gualberto Gussoni[4], Oriana Ciani[5]

Digital therapeutics, HTA and reimbursement in Italy

This chapter provides information and proposals with a view to promoting digital therapeutics (DTx) awareness and culture in Italy, and activating procedures for scientific assessment, access and reimbursement policy in relation to this domain.

In some European countries, as described elsewhere in this volume, different procedures have been activated for access and reimbursement policy in relation to DTx. However, no overall coordination is applied to these isolated initiatives: application of uniform procedures in the different European countries presupposes addressing the still completely unfulfilled need for a policy framework on legislative and regulatory matters, health technology assessment (HTA), access and reimbursement.

On the following pages, a number of fundamental considerations are discussed in relation to technological assessment and reimbursement of DTx:

1. DTx - Regulatory framework;
2. DTx - Regulatory pathways for assessment and reimbursement;
3. DTx and health technology assessment - HTA;
4. DTx in Italy and the National Plan for Chronic Care.

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1. DTx - Regulatory framework

A coherent, shared European framework would provide regulatory and procedural clarity regarding development of DTx, authorization procedures, assessment criteria and methods, and access and reimbursement procedures. These procedures vary within the different welfare systems of European countries - an example being the specific case of Italy, where the national health service and essential levels of care exist side by side.

DTx in Europe are currently subject to the new Regulation (EU) 2017/745 of 5 April 2017 on Medical Devices, superseding Directives 90/385/CE (active implantable medical devices) and 93/42/CE (medical devices) and fully applicable from May 26th 2021[(1)].

The EU Regulation does not deal specifically with DTx, since it was conceived and drafted before the concept of their availability for medical prescription saw the light of day. In addition, a basic question that remains unaddressed in Italy is whether DTx (given that they are defined as medical devices) fall exclusively within the purview of the Ministry of Health's General Directorate of Medical Devices and Pharmaceutical Services, or related HTA and reimbursement issues are the domain of the Italian Medicines Agency (Agenzia Italiana del Farmaco - AIFA). This difficulty in establishing a clear-cut regulatory and procedural borderline between medical devices and drugs becomes even more problematic where a DTx product is designed for use in combination with a drug.

2. DTx - Regulatory pathways for assessment and reimbursement

To safeguard the patient's health and ensure the best conditions of use for DTx, it is fundamental to understand what is the optimal method for testing them and thus, irrespective of the technology involved, what are the required regulatory pathways for assessment and approval.

The new Regulation (EU) 2017/745 requires that medical devices must be not only safe but also clinically effective. In particular, it states in Article 2 (points 52 and 53) that the medical device must be characterized by:

- **clinical performance** - i.e., the ability of a device, resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its in-

tended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for patients, when used as intended by the manufacturer;

• **clinical benefit** - i.e., the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health.

The 2017/745 text refers to clinical investigation for purposes of documenting this benefit. However, unlike the requirements for drugs, the Regulation does not specify whether investigation must be experimental or observational, nor does it state what must be the characteristics of clinical trials. Working groups and technical committees are looking into these questions at European level, so that guidelines regarding the qualitative standards to be assessed in clinical trials can be formulated on the basis of the device's classification - e.g., high-risk implantable devices.

We think that the same level of detail is also required for DTx, to ensure that the CE mark can be awarded only on the basis of confirmatory clinical experimentation, thus based on methodology (randomized, controlled trials), sample size, duration of treatment and of any follow-up. In other words, the same criteria should apply as for assessment of pharmacological treatments. A general requirement for "clinical investigation" does not in itself mitigate the risk of awarding the CE mark inappropriately - e.g., on the sole basis of clinical data obtained in a setting that might be limited to exploratory, not confirmatory clinical trials. In all cases, the research protocol must be available for inclusion in a register.

In terms of therapeutic aims, a digital antidepressant does not differ from chemical antidepressants, and the same can probably be said of its position in the therapeutic pathway. The probable scenario for the near future is that the physician will prescribe a digital antidepressant instead of - or in addition to - a chemical antidepressant. Though the mechanism of action is completely different, the fact that the active principle is chemical or digital makes no difference to the intended therapeutic effect, this being to reduce the severity or symptoms of the depressive state. The nature of the active principle responsible for the therapeutic effect is secondary to the therapeutic aim. For this reason, the doctor expects both antidepressants (irrespective of the technology that supports their effect) to give the same guarantee of efficacy and tolerability. It is not acceptable to move towards a situation where only the chemical form - not the digital variant - can be confidently prescribed. Against this background, evidence collected for DTx cannot be inferior to that for a standard pharmacolog-

ical therapy. Irrespective of the active principle's nature and the regulatory pathway, clinical evidence must therefore be the same, both in quantitative terms and with regard to the methodology underlying its generation.

It is also fair to expect that, where the health system reimburses a chemical antidepressant, it should equally reimburse the equivalent digital antidepressant, subject to there being no difference in terms of efficacy and tolerability.

It is necessary to avoid a situation where different assessment pathways, based on the nature of the element responsible for the therapeutic effect and not on the aim of the treatment, might prove counterproductive with a view to the ultimate prospect of benefit for the patient. It is also necessary to ensure, in the context of a given indication, that the therapeutic value of DTx is not underestimated in the hierarchical scale of possible treatment options. This need underpins a solid rationale for extensive training activity involving doctors. In the final analysis, a failure to recognize the usefulness of DTx in the overall setting of available treatments could be damaging to the patient, who could, in some cases, be deprived of a therapy as effective as the drug and probably better tolerated.

We consider it necessary, for all cases in which reimbursement is required for DTx, that the therapy be dispensed by prescription and used under medical control. The doctor, if authorized by the patient, must be able to monitor the progression of the treatment. This can be done by means of a dashboard housed on the physician's personal computer.

There is a further aspect worthy of consideration. In some cases, a DTx product developed and authorized in specific healthcare settings (e.g., the USA or Asia) could be made available in a European context without likelihood of differences in terms of outcome, and thus benefit from a simplified pathway to authorization and reimbursement. However, there may be DTx products for which the transferability to Europe/Italy of evidence collected in different healthcare, epidemiological and cultural settings could be doubtful (e.g., in the case of treatments for mood disturbances, neurodevelopment, psychoses or chronic pain). In such cases, it can be hypothesized that a European health authority assessing possible authorization of a DTx product can ask the manufacturer for extra documentation. This would involve arranging for investigations to be carried out locally, based on a process of transcultural adaptation similar to that used for methodological tools like quality of life questionnaires, allowing proper documentation of the product's effective digital "bioavailability".

Currently, a national Digital Therapeutics Observatory is being set up in Italy, to allow registration and subsequent assessment of research and

clinical trial protocols for experimental DTx, as well as for such products as will already have been authorized in Italy. The aim is to ensure that the doctor and the patient have appropriate guarantees regarding the consistency between clinical development and the manufacturer's indications, as well as the appropriateness of the related promotional claims.

3. DTx and health technology assessment - HTA

Every new health technology - including DTx - is subject, once it has rceeived regulatory approval, to health technology assessment (HTA). This assessment becomes necessary today in order to determine digital healthcare technology's therapeutic value and position in the treatment pathway, with a view to ensuring that informed decisions are taken on procurement, reimbursement and use.

The concept of health technology is broad, embracing as it does healthcare equipment, medical devices, drugs, diagnostic systems, medical and surgical procedures, healthcare pathways, and the structural, organizational and managerial models through which care is delivered. These technological domains thus embrace all practical applications of healthcare knowledge, including DTx, that are used for promoting health and for preventing, diagnosing or treating disease.

HTA comprises systematic, multidisciplinary evaluation, taking in the description, examination and appraisal of healthcare, as well as the short- or long-term economic, social and ethical implications directly or indirectly related to existing and newly introduced health technologies. In the case of emerging health technologies such as DTx, the need for this assessment within the setting of clinical practice becomes even more critical and relevant.

For the healthcare systems and payers, it is neither right nor acceptable to consider that a new form of health technology can automatically be equated with therapeutic innovation. It is therefore necessary to establish an individual DTx product's therapeutic added value, the associated health gain for the patient, the budget impact and the cost-effectiveness profile. In a setting of limited resources and growing needs, it is fundamental to invest efficiently, in other words maximizing benefits and minimizing costs.

AIFA, for example, assesses the degree of innovativeness brought by a drug, adopting criteria such as therapeutic need, therapeutic added value and quality of evidence[2]. The Ministry of Health, in collaboration with AIFA, the Italian Agency for Regional Healthcare Services (*Agenzia Nazionale per i Servizi Sanitari Regionali* - AGENAS) and representatives of the regions,

published a very detailed national HTA programme in February 2019[3].

In this regard, we agree with the precept that the study methodology for assessing the efficacy and therapeutic value of DTx must be largely based on high-quality, controlled clinical trials[4]. These must be robust, complying with the standards of evidence-based medicine and the best available published methodologies. Another useful reference point is the extension of Consolidated Standards of Reporting Trials (CONSORT) to web-based interventions[5].

Available experience is still limited. In Europe, it is essentially confined to assessments carried out in Germany as part of the BfArM-run DIGA programme, and above all the work done in the UK by the National Institute for Health and Care Excellence (NICE) on the DTx products *Deprexis*[6], for treatment of depression, and *Sleepio*[7], for treatment of insomnia.

Analysis of the NICE reports can offer useful indications for development of a structured HTA model, specifically tailored to DTx.

The document *Deprexis for adults with depression* is the first example of HTA on DTx[6]. It consists of a summary and the following four sections:

Technical assessment
- Digital technology and its indication
- Regulatory status
- Current usage
- Current therapeutic pathway
- Field of application of digital technology
- Population, setting and intended user
- Place in therapy
- Equality considerations

Content
- Care model
- Outcome measures
- Content assessment
- Scalability
- Technical standards

Clinical evidence
- Proof of clinical efficacy
- Overall assessment of proof of efficacy
- Main elements of proofs of efficacy and related doubts

Cost and resource impact
- Technology costs
- Economic impact compared with the standard of care
- Potential impact on healthcare resources

4. DTx in Italy and the National Plan for Chronic Care

In Italy, a specific sector of particular interest for application and reimbursement of DTx is that of care pathways (CPs), in the broader context of regional and national care planning for chronic patients[8] and the new system for guarantee of essential care levels (*Nuovo Sistema di Garanzia dei Livelli Essenziali di Assistenza*/NSG-LEA)[9].

Based on the aims set out for testing indicators included in CPs and envisaged within the NSG-LEA, five test areas have been chosen for implementation, assessment and reimbursement of DTx. These are chronic obstructive pulmonary disease (COPD), diabetes, heart failure, female breast cancer and tumours of the colon-rectum.

A particularly interesting proposal is that DTx products of proven efficacy, selected by a HTA process, should be placed within CPs. This would involve setting up a new CP, starting by disassembling the existing one and then reassembling it with the selected DTx. For instance, the document could be selected from the PDTA Net database, a project of the *Fondazione ReS* that also enables detailed analysis of the CPs[10].

In operational terms, the aim would be to identify, for each of the reassembled CPs related to the disease in question, the therapeutic value of the DTx under assessment. This would involve comparing the CPs, with and without DTx products, by indicators of process and outcome.

This process will therefore comprise two main stages:

- a methodological stage, illustrating the rationale and method for the proposed place in therapy of the selected DTx in the CP, the choice of specific indicators, the digital biomarkers used, frequency of use, and data collection methods;
- an operational stage, in collaboration with local health authorities, to generate evidence for definition of the digital technology's therapeutic value. Based on impact analysis regarding adherence to therapy, as well as emergency department and hospital admissions, this assessment would be carried out either on a case-control basis or by means of other methodologies.

Finally, it must be pointed out that the enormous boost to the use of digital

technologies in Italy resulting from the CoViD-19 pandemic is a facilitating factor for access to - and implementation of - DTx. Indeed, the Italian government's recent Recovery Plan 2021[11] envisages strengthening of community-based prevention and care (proximity networks, facilities and telemedicine), guaranteeing equal access to treatment and healthcare services, and promoting innovation and digitalization within the Italian National Health Service. Funding of €15.63 billion has been earmarked for this purpose. The extent and the specific settings of the funding are particularly important, with a view to development and reimbursement of DTx.

5. Conclusions

Digital technologies offer an unprecedented opportunity to bring the necessary changes so that future development of European healthcare can have a sustainable basis, while also improving patients' health outcomes.

Creating an environment that places a premium on innovation in the field of digital health is fundamental. Policymakers must give a clear signal to patients, healthcare professionals, suppliers and manufacturers, underlining that digital technologies are an integral part on the future healthcare scenario in Europe. It will be of fundamental importance to rethink questions underpinning reimbursement and funding systems, in order to guarantee a stable, clear route to market for digital innovations.

Awareness raising on experience to date and on best practices can help to demonstrate that some payers in Europe have already envisaged conditions enabling digital instruments, like connected devices and telemedicine, to occupy a meaningful place in clinical therapy. Recognizing and disseminating awareness of the already available models can help to build trust in the entire system. It can also inspire Italy to draw benefits from the best of the experience acquired in neighbouring countries, adapting them to the specificities of the national market and healthcare scenario.

Essentially, we propose:

- greater regulatory detail at EU level with regard to clinical investigation of DTx, so as to guarantee that devices used for therapeutic purposes are subject to the same standards of efficacy and safety as drugs;
- adoption of a HTA model, similar to that proposed by NICE, to be adapted and further developed for the Italian setting;
- a comprehensive review of the instruments available in Italy to finetune ac-

cess and monitoring in relation to drugs and technologies, with a view to identifying the best ways of safeguarding the patient in achieving the expected therapeutic effects of DTx, set within an array of multiple potential therapeutic options;

- clear definitions of authorization and indication for use of DTx, at European level and within the specific setting of Italy, with legislative provision for setting up of a dedicated commission within the Ministry of Health's General Directorate for Medical Devices and Pharmaceutical Services, thus enabling proper assessment of DTx, negotiation for reimbursement and their inclusion in essential care levels.

What is known

- DTx come within the definition of a medical device, subject to the provisions of Regulation (EU) 2017/745 on medical devices
- Regulation (EU) 2017/ 745 contains no specific provisions regarding DTx
- Regulation (EU) 2017/745 requires that medical devices must be not only safe but also clinically effective, meaning that the past emphasis on safety alone is now shifted at least in part to efficacy
- Faced with the availability of DTx options, the doctor will insist that these must give the same guarantees of efficacy and safety as existing treatment methods
- There are existing frameworks for the evaluation of DTx, such as the one developed by NICE
- DTx can already be reimbursed by the French and German health services, by means of specific procedures.

What is uncertain

- What must be the characteristics of clinical investigation for DTx? What proof of efficacy must be generated in order that the CE mark be awarded to a DTx product? The same as for a drug?
- In Italy, if a DTx product with a CE mark covers the same therapeutic indication as a reimbursable drug, does it benefit from the same reimbursement conditions? What regulatory pathway is applicable in such cases?
- Who establishes, for DTx, the need for a medical prescription?

What we recommend

- Detailed regulatory provision at European level (for example, in the form of an addendum to the EU Regulation) in relation to specific clinical investigation for DTx, in such a way as to guarantee that a device used for therapeutic purposes is subject to standards of efficacy

and safety comparable with those applied to drugs
- Authorization and indication for use should be defined at European level
- Development and adoption of a risk-based evaluation framework, similar to that proposed by NICE, which would be useful for national HTA purposes.

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Digital therapeutics, prerequisites for development of the technological and economic ecosystem in Italy and Europe

Digital therapeutics, as a new medical intervention method and therapeutic option for the patient, can enhance outcomes of chronic diseases and dependencies(1). They also afford a novel opportunity, particularly relevant in light of the new normal resulting from CoViD-19, for development of Italy's and Europe's technological and economic ecosystem.

The development of digital therapeutics is ushering in an emerging health market that is constantly growing, with new actors and new rules (definition and discussion of which are still, to a certain extent, work in progress). The only viable competitors on this new market will be those based in countries that have created an environment conducive to development and innovation, in terms both of products and of organizational models(2).

Digital therapeutics and the market

Estimates of market size and trends in the next 10 years have been the subject of considerable investigation by specialized research groups, whose conclusions in most cases are fairly consistent.

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The global market for digital therapeutics was worth $1.7 billion in 2019. According to current estimates, it could reach $9.4 billion by 2028, with a compound annual growth rate (CAGR) of 22.1% between 2020 and 2028[3]. Other estimates indicate that the $9 billion threshold can be reached as early as 2025, and that use of digital therapeutics by patients will have grown more than tenfold by 2023[4].

Among the major global determinants of market growth for digital therapeutics are the increasing need to control health costs related to higher incidence and prevalence of chronic diseases, development of disease management models in which the patient takes on a progressively more active role, the increase in missed diagnoses, and the reduction in lead time for a correct diagnosis. Further factors are the more widespread use of interactive devices (smartphones and tablets), the development of health(care) applications, and the growing number of partnerships or collaborations between pharmaceutical and technological companies. However, these growth factors are offset by other considerations that can slow down or hinder adoption of digital therapeutics and the related market growth - particularly in relation to provision for patients' personal data protection, and the overarching issue of risks and threats to information security. Other limiting factors, particularly in Italy, are the low awareness of these new therapeutic tools and, more generally, the poor digital literacy of the population at large, as well as pushback from some providers of traditional health services.

Market segmentation

Segmentation of the global digital therapeutics market is mainly by therapeutic indication and distribution channel.

In terms of indications, the market breaks down as follows:

- metabolic diseases
- cardiovascular diseases
- central nervous system diseases
- respiratory diseases
- smoking cessation
- musculoskeletal diseases
- renal diseases
- other.

Metabolic diseases (particularly type 2 diabetes) are the segment with the potential to grow fastest and to achieve the greatest increase in the next five years. The growing prevalence of diabetes contributes to the increas-

ing demand for digital therapeutics, and is one of the main development factors for this market.

In terms of distribution channel, the digital therapeutics market breaks down into the following segments:

- patients (B2C - *Business to Consumer*)
- health service providers (B2B - *Business to Business*)
- private sector payors, such as insurance companies (B2B - *Business to Business*)
- public sector payors, such as regional or national health services (B2G - *Business to Government*, or B2A - *Business to Administration*)
- employers (B2B - *Business to Business*).

B2B is currently the sector with the largest market share and the highest expected CAGR. This trend (particularly in the USA, which will continue to be the leading country in the development of digital therapeutics over the next few years) is related to growing uptake of digital therapeutics by health service providers and private payors, as well as by employers running employee benefit schemes.

In Europe, and particularly in countries with mainly state-financed health services such as Italy, increasing use of digital therapeutics and related market growth will be dependent on development of B2G models, enabling widespread access and reimbursement by public health services in the same way as for drug treatments[5].

Territorially, North America is currently the largest market in the world, thanks to growing investments in digital therapeutics, the large and ever-increasing number of start-ups in this field, and the government support that gives them a decisive boost[6].

The European digital therapeutics market was valued at $503.48 million in 2018, and is expected to reach $2.3 billion by 2026, with a CAGR of 20.6%[3].

Various surveys agree that emerging markets such as Brazil and India can offer market players significant growth opportunities[3,4].

International companies

The major players in this sector are mostly located in the USA, and to a far lesser extent in Europe and elsewhere. Some of the companies currently to the fore in digital therapeutics are listed in *Table 1*.

Table 1 - Major digital therapeutics companies across the world

Company	Country	Areas of interest
Pear Therapeutics	USA	Dependencies, chronic insomnia, schizophrenia, depression
Akili Inreactive	USA	Attention Deficit and Hyperactivity Disorder (ADHD), Autism
Omada Health	USA	Diabetes, hypertension, muscle and joint pains
WellDoc	USA	Diabetes, insomnia
Livongo	USA	Diabetes
Noom Health	USA	Obesity
Cognoa	USA	Autism
Better Therapeutics	USA	Cardio-metabolic diseases
Mahana	USA	Irritable bowel syndrome
DarioHealth	USA	Diabetes
Wise Therapeutics	USA	Stress, anxiety
Click Therapeutics	USA	Depression, schizophrenia, insomnia
Meru Health	USA	Depression
MetaMe Health	USA	Irritable bowel syndrome
GAIA	Germany	Depression
KAIA	Germany	Musculoskeletal pain, chronic obstructive pulmonary disease
M Sense	Germany	Migraine
Voluntis	France	Oncology, diabetes
Shleep	Netherlands	Insomnia
Oto	UK	Tinnitus
Sivan	Israel	Oncology
Wellthy	India	Diabetes, obesity, heart failure, asthma, dyslipidaemia, hypertension
NeuroGlee Therapeutics	Singapore	Alzheimer's, mild cognitive impairment
CuresApp	Japan	Nicotine dependency

Most of the well established, larger digital therapeutics companies belong to the Digital Therapeutics Alliance (DTA), a non-profit association founded in 2017. The DTA comprises leading specialist companies and other stakeholders committed to development of digital therapeutics, with an international focus on the digital therapeutics business, their head office in the USA and a section dedicated to Europe. The mission of the DTA is to disseminate knowledge and use of clinical research-based digital therapeutics, and their integration into care pathways, by means of training; and to broaden the understanding, adoption and integration of clinically evaluated digital therapeutics with patients, clinicians, payors and policymakers, through education, advocacy, and cross-industry collaboration, the ultimate aim being to enhance clinical and economic health outcomes[8].

Digital biotech companies in Italy

The primary actors in research, development and market placement of digital therapeutics in Italy are innovative start-ups, which intervene in different capacities at the various levels of the digital therapeutics development chain. These are companies that - in their own right or through strategic partnerships - integrate and organize the entire supply chain, from software design and development to implementation of the clinical programme and market placement. As such, they can be defined as digital biotech companies.

To fulfil this definition, the companies concerned must explicitly declare that they document the therapeutic value of their products on the basis of confirmatory evidence obtained from randomized, controlled clinical trials.

In other cases, the companies concerned are specialized in specific technological activities, such as the development of serious games, of virtual reality, or of digital excipients. In these cases, it is the collaboration with digital biotech companies, as defined in the previous paragraph, that qualifies the actors concerned for inclusion in the category of digital therapeutics companies.

Despite their limited size in quantitative terms, digital biotech companies work in close contact with the academic world and are primary centres for innovation and knowledge production, enabling dissemination of know-how for purposes such as education. By maintaining close contact with international research groups and companies, digital biotech companies contribute to the overall development of Italy's advanced knowledge-based ecosystem.

However, this development is currently limited by the absence of clear regulatory guidelines regarding access to digital therapeutics, above

all in terms of eligibility to be classified as such, reimbursement policy and the related conditions.

A survey carried out via LinkedIn, in October 2020, looked at Italian companies involved in various ways in digital therapeutics R&D and delivery. *Table 2* shows the companies concerned, two of which are included in the list of 1000 International digital health companies[8].

Table 2 - Digital therapeutics companies active in Italy

Digital therapeutics companies		**Specialized companies**	
Italian companies	***Italian operations***	***Company***	***Area of interest***
daVinci Digital Therapeutics srl [8]	Amiko Health Ltd[8]	Imaginary srl	Serious games
Kerubin srl	Amicomed Inc	Helaglobe srl	Serious games
Digital Rehab srl		Restorative Neurotechnologies srl	Serious games
daVi DigitalMedicine srl		Softcare Studios srl	Serious games

Pharmaceutical companies and digital therapeutics start-ups

Digital therapeutics have been seen by some as a potential threat to pharmaceutical companies, for which the perceived danger is that they could find themselves relegated by digital technology companies into a position of disintermediation vis-à-vis the patient[9].

We take the opposite view and consider digital therapeutics as an important new opportunity for pharmaceutical companies, thanks above all to the added value they offer the patient on drug treatment[10]. In this regard, collaboration towards development of new digital therapeutics products can offer pharmaceutical companies a number of benefits:

- improvement of health outcomes for the patient
- enhanced value of the drug
- extension of the drug's life cycle
- access to real-time/real-world information
- personalization of drug treatment
- completion of the therapeutic armamentarium
- entry into new therapeutic areas.

Use of digital therapeutics by the patient generates a considerable

quantity of data, related both to the disease under treatment and to the therapies used (digital, pharmacological, other). These are real-world data, generated by interaction with the digital therapeutics algorithm, by completing a questionnaire or by providing information; real-time data can also be relayed from a sensor or device used by the patient. If authorized by the patient in accordance with current regulations, real-world/real-time data on the drug can be shared with the pharmaceutical company, which thus has immediate access to a far greater quantity of data than those generated during clinical development.

Given these opportunities, a number of pharmaceutical companies in the last few years have entered into collaborative agreements with technological companies for development of digital therapeutics *(Table 3)*.

Table 3 - Collaborations between pharmaceutical companies and technological start-ups for development of digital therapeutics

Technological company	Pharmaceutical company	Year	Therapeutic indication
GAIA AG	Servier	2015	Major depression
Voluntis	Sanofi	2017	Diabetes
Click Therapeutics	Sanofi	2018	Various
Pear Therapeutics	Novartis	2018	Schizophrenia
Voluntis	AstraZeneca	2018	Oncology
Voluntis	Abbvie	2018	Autoimmune diseases
Akili Laboratories	Shionogi	2019	ADHD - ASD
Click Therapeutics	Otsuka	2019	Major depression
Voluntis	Novartis	2019	Oncology
Noom	Novo Nordisk	2019	Obesity
Wellthy Therapeutics	Bayer	2019	Various
Welldoc	Astellas	2019	Diabetes
Voluntis	BMS	2020	Oncology
Click Therapeutics	Boehringer Ingelheim	2020	Schizophrenia
Kaia Health Software	Chiesi	2021	COPD

ADHD - Attention Deficit Hyperactivity Disorder; ASD - Autism Spectrum Disorder; COPD - Chronic Obstructive Pulmonary Disease

Digital therapeutics, Italy and Europe

To date, no digital therapeutics product is available in Italy and no Italian digital biotech company has yet completed development of one in its own right, though the first digital therapeutics trials are now starting.

Digital therapeutics are nevertheless a major opportunity, both for Italy and for Europe. Italy, in particular, gives full expression to its excellence in the workroom, in the micro-company and in the small and medium enterprise, where R&D needs can be met by investments from within the Italian system. The entrepreneurial spirit and creativity that are the traditional strengths of the Italians thrive in small-scale initiatives, often in niche sectors. Examples are fashion, cars, motorcycles, shoes and other sectors where technology goes hand in hand with business flair, bearing witness to Italians' aptitude and skills. All these features are present in the new digital therapeutics ecosystem, enabling Italy to act as a front runner in a way that would be hardly imaginable in other research sectors.

In order for Europe and Italy to be able to take on a leading role in this emerging area of digital technology and healthcare, it is first and foremost up to institutions, but also companies, investors, patients and representatives of civil society to align their interests, identifying digital biotechnology as a strategic area for the countries. It is only by joint effort that digital biotech and pharmaceutical companies will together be able to research, develop and sell new digital therapeutics products, and new combined drug digital therapies, on a worldwide market, therefore offering a better response to the patient's expectations and contributing to the economic and social development of our continent. In this perspective, the fact the digitization as a whole has been considered one of the main missions of the post-CoViD-19 Recovery Plan outlined by the European Commission represents an important signal that must be adequately exploited.

What is known

- DTx are a new market
- The expected size of this market in 2028 is estimated at $9.4 billion, with a CAGR of 22.1% between 2020-2028
- The European DTx market is valued $503.48 in 2018 and is expected to reach $2.6 billion by 2026
- The DTx market in Italy is still non-existent

- Many companies (particularly based in the USA) are entering this market
- A number of DTx companies have been set up in the last few years in Europe and in Italy.

What is uncertain

- In the specific case of Italy, how can a DTx product become eligible for reimbursement?
- How can promotion of DTx be achieved in Europe and in Italy?
- How can a company ensure access and reimbursement for a combination between one of its drugs and a DTx product?
- How can European countries support international development of their DTx companies?

What we recommend

- In countries where this has not yet happened (for example Italy), define simple, clear rules for DTx, in relation to arrangements for access, reimbursement, scientific information and promotion
- Promote development of new European digital companies and sustain development of existing ones, by means of incentives, competitive bidding and dedicated initiatives
- Promote training programmes for doctors, both GPs and specialists, regarding digital medicine in general and DTx in particular
- Digitization is one of the main missions of the European Recovery Plan post-CoViD-19: efforts are needed to ensure that investments in this area are also significantly directed towards the life sciences.

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Enabling organizational conditions for digital therapeutics in Italy

1. Digital therapeutics for Italy: economic and industrial background

In the last decade, the economic crisis of 2007 and the subsequent public sector budget cuts of 2011 and 2012 have affected availability of funding for healthcare and, more generally, for life sciences as a whole. Even today, if Italian healthcare spending is compared with that of the main national economies in Europe, there is a clear shortfall. The Organization for Economic Co-operation and Development (OECD) data show that in 2018 Italian healthcare spending was about € 2,900 per capita on an economy-wide PPP basis - far less than in Germany (1.75 times higher than the Italian figure), France (1.45 times higher) and the UK (1.18 times higher).

However, the Italian national health service (*Servizio Sanitario Nazionale* - SSN) has successfully maintained high healthcare standards and quality of life (albeit with clear differences between different parts of the country), keeping these at a "competitive" level in international terms. These results have been grounded on good practices, as well as greater user awareness and involvement (participatory quality assessment, etc.), dialogue and cooperation between healthcare administrators and Patients' Organizations, and the impact of public and private research and innova-

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[6]*European Patients' Academy/EUPATI Non-Profit Organization*

tion. This has borne fruit, as seen in the 2018 life expectancy figure of 83.4 years, among the highest in the world after Japan, Switzerland and Spain. Healthy life expectancy in Italy is 73.2 years, which is again higher then the mean figure for Europe and for countries like the USA, where healthy life expectancy at birth is 68.5 years[1]. Since the current pandemic will obviously impact these important demographic indicators, at least in a long-term perspective, the national health service can safeguard and further enhance them only if it can count on a well organized strategy in line with certain fundamental principles. These include a more uniform response to the population's health needs, in terms of appropriateness, efficacy, efficient use of resources and sustainability of the SSN itself.

A possible support and ally for modern health systems is digitalization, whose potential today is almost unrecognizable by comparison even with 20 years ago, paving the way for use of artificial intelligence-based models and predictive algorithms. As recognized *inter alia* by the World Health Organization, digital health offers a possible response to the need for improved healthcare access, reduction of related costs, improved quality in health management and self-care, and more effective, personalized healthcare provision. According to the WHO, digital health can help to reduce global health inequalities provided that certain priorities are addressed: patients' and caregivers' level of digital literacy must be taken into account, with planning and implementation of initiatives to address any shortfalls in this respect; healthcare professionals' workload must also be factored in, and delivery of healthcare and related social services made more efficient. This vision has already received significant plaudits and its relevance has been underlined by the dramatic health emergency triggered by CoViD-19, which has placed health services worldwide under unprecedented pressure. In this regard, the Italian Institute of Public Health (*Istituto Superiore di Sanità*) has identified digital health systems as allies for optimizing health emergency management and guaranteeing care for the population, particularly for medically fragile subjects and those with chronic illnesses[2].

The broader context of digital health includes the innovative category of digital therapeutics (DTx), which are already an integral part of the healthcare services on offer in the United States and some European countries. DTx should be seen as a strategic tool for Italy, for three main reasons: they could favour clinical efficacy, *inter alia* by promoting new forms of patient and caregiver engagement; they could open up a new area of de-

velopment for the Italian life sciences sector; and, potentially, they could afford a useful contribution to the SSN's efficiency and sustainability. Italy, in addition to introducing DTx into its medical practice, has the credentials to become an international hub in their development and manufacture. These credentials are as follows:

1. The digital health and DTx sector comprises mostly small and medium enterprises (SMEs) with strong territorial connections, particularly suited to research and development of innovative systems thanks to their lean organizational structure, based on a handful of highly specialized professionals.

2. Thanks to their strong territorial connections (health ecosystem, according to the quadruple helix innovation model), SMEs help to cut down the distance between healthcare, patients and industry, to ensure ready availability of innovative solutions in response to specific community needs, and the setting up of operational networks for development of innovative research projects.

3. SMEs, on which the medical devices sector in Europe is strongly dependent, account for over 90% of Italy's entrepreneurial fabric, with an overall figure of 5 million companies and over 15 million employees (82% of the total for Italy as a whole)[3].

4. Since 2015, public expenditure in support of SMEs in Italy has increased: they now receive about 70% of overall national subsidization (reference period 2012-2017), accounting for a total of € 2.23 billion in 2017.

5. Italy is a pole of excellence both in information and communication technologies (ICT)[4] and in life sciences, a sector that accounts for 10% of Gross Domestic Product (GDP) in terms of added value[5].

The scenario outlined above indicates that the Italian system is particularly conducive to collaboration between multidisciplinary teams, able to develop innovative solutions. This means fulfilment of another fundamental requirement for development of DTx - an ecosystem with healthcare and social services able to participate actively in development processes, complemented in the life sciences and digital sectors by institutions and enterprises that boast excellent credentials in terms of operational productivity. In addition, potential synergies must be appropriately leveraged between small, agile start-ups and larger companies (big pharma and big tech), with a view to boosting innovation by complementing the advantages of specialization and creativity with economies of scale and access to wider markets. The presence of major players from the digital and ICT world can be an asset for the territory, bearing in mind the trend in terms of healthcare sector investment by

companies like Google, Apple and Amazon. However, taking full advantage of such opportunities presupposes targeted policies to safeguard the final user's privacy and data security.

A lot thus remains to be done in regulatory and organizational terms, a case in point being the difficulty of making digital solutions interoperable with currently used (and significantly different) digital and data collection systems - not to mention the basic infrastructure shortcomings. Nevertheless, in Italy both the entrepreneurial and research fabric and the networks of close links with the communities concerned lend themselves to the development of a sector dependent on high-level skills (together with the entrepreneurial dynamism of SMEs and a structural ecosystem conducive to collaboration), and on an overall setting in which technology can be experimentally developed.

Looking at the current scenario, it should be noted that the strategies and programmes of the European institutions share the aim of creating greater synergies between the healthcare and digital sectors. Recently, to incentivize the sector's development at European level, EIT-Health (one of the knowledge and innovation communities set up by the European Institute of innovation and Technology - EIT) included digital health among the sectors eligible for access to the first pan-European crowdfunding platform dedicated to the health field. In addition, Horizon Europe, a new European programme for research and innovation, gives particular emphasis to boosting already active cross-cluster complementarities between the "health" and "digital, industry and space" clusters, through initiatives, calls and existing or new public-private partnerships. These initiatives are particularly significant, as they include *inter alia* participatory models for active involvement of EU citizens in European research and development processes - e.g., the "Large-Scale Innovation and Transformation of Health Systems in a Digital and Ageing Society" partnership, whose launch is scheduled for 2021. In the mid to long term, these programmes could favour the consolidation of a new manufacturing and research sector dedicated to digital health, and to DTx in particular, both in Italy and in Europe as a whole. Complementing these initiatives are the working instruments made available by the EU, such as precommercial procurement in phase 0, giving patients and caregivers an opportunity to participate directly in the definition of the health needs profile. This process enables generation of a solid basis on which to build phase 1, thanks to which the profile identified by the stakeholders is passed on to companies, thus optimizing management of the R&D pipeline.

Finally, another major enabling factor for this digital revolution in the health sector is the important wave of European investments that have been activated in support of national economies. These are based on the plan agreed by the European Commission, the European Parliament and national leaders, the aim being to create the foundations of a modern and more sustainable Europe, prioritizing *inter alia* healthcare and digitalization. Next Generation EU required all countries receiving these funds to draw up national recovery and resilience plans, so as to ensure appropriate planning and identification of the areas in which each member state proposes to invest the EU funds earmarked for this purpose. Funding made available to Italy in this way will total €110 billion, to which a further 90 billion should be added, of which it is estimated that about 20% will be dedicated to digitalization of national systems, including the SSN. This is a major step forward, which could generate a paradigm shift and bring policy-makers and legislators to work towards smoothing the path for integration of digital innovation into all sectors (manufacturing, services, trade). A major opportunity can thus be envisaged for Europe and for Italy, conducive to investment in the future of healthcare and to development of a regulatory, infrastructure and organizational setting able to guarantee the development of digital health in Italy and reinforce the country's position internationally.

2. DTx: enabling organizational conditions

Speaking of organizational conditions enabling an ecosystem conducive to the success of DTx means that the following steps must be taken:

1. enhance knowledge related to the efficacy, safety and mechanisms of action of DTx (e.g., by activating lifelong learning programmes for digital skills);

2. raise awareness of them, as an available and effective alternative to current treatments;

3. develop the necessary capacities for appropriate use of DTx, and their integration into existing diagnostic therapeutic pathways and information flows;

4. focus on the interest, usefulness, cost-effectiveness and full potential of DTx, and be prepared to demonstrate them;

5. clearly define decision-making processes (in relation to regulatory requirements, prescription and reimbursement), and the regulatory framework required for implementation and adoption of the related technology.

All these conditions, which might have seemed difficult to achieve in a shorter timeframe until only a few months ago, now seem to be more readily achievable as a result of the CoViD-19 emergency, which in the space of a few months prompted successful experimentation with telemedicine systems, in the broad sense of the term, and meant that digital technology was given the chance to prove its worth in the health sector.

The first of the points listed above is discussed in detail elsewhere in this volume. For the purposes of this chapter, what should be emphasized is the importance of extensive and generalized training for a large population of healthcare professionals in the various sectors where DTx can be used. It will also be necessary to ensure that appropriate provision is made for introduction of new job titles, so that healthcare professionals and users can find ready interlocutors to help them address such issues as choosing among different DTx products (software packages) with the same aims and fields of application, or monitoring their use and troubleshooting for any IT problems. Data analysts will also play a major role, given that the vocation of DTx is largely to generate enormous quantities of data and information. Hence the need for specific job profiles encompassing these emerging skills: while the people with this know-how can obviously come from a variety of professional backgrounds, their training and experience should be appropriate to a strongly interdisciplinary vision. This means embracing a broad range of medical, engineering, psycho-behavioural, economic and managerial priorities, with an appropriately open approach to addressing "complex" problems.

Information must be shared with all concerned, requiring outreach to patients, caregivers, health administrators, top managers, policy-makers and, more generally, all those who could benefit from the availability of DTx in clinical practice. In addition, a fundamental requirement is the involvement of Scientific Societies, able to:

- promote the dissemination of innovative health products, services and approaches, DTx being emblematic in this respect;
- guarantee that DTx comply with the norms and requirements of modern, evidence-based medicine;
- draw up guidelines, where appropriate, for their correct use.

Today, the potential of DTx is still little known - all the more so, if one thinks that Italy generally lags behind in terms of digital literacy and readiness to make the best use of all the related opportunities. Involvement of patients and raising of their awareness are particularly important, through

targeted actions to show the potential benefits of DTx, *inter alia* by comparison with other treatments; to this end, major points to emphasize are, on the one hand, the patient's autonomy in managing treatment and, on the other hand, the safety provided by their remaining in continuous contact with the physician and a team of experts. The required awareness-raising activities will depend on qualified people, able to explain in detail the unique features of DTx, the fields of application in which they can be potentially effective and the settings in which they have already been applied: this requires excellent communication skills, with the ability to explain concepts clearly, engagingly and effectively. The ability to adapt to different audiences is also of fundamental importance, ensuring that the most convincing and effective arguments can be used to address any doubts or scepticism. This awareness raising is generally the brief of professional communicators or trainers from outside the public healthcare system or its private sector counterparts, who have already undertaken similar work for the manufacturers and have an excellent track record in terms of credibility and reliability. What must be avoided, however, is the involvement of speakers who can offer nothing more than facile support for innovation, able to see only its advantages but blind to any practical limitations and difficulties - or, even worse, trainers with a style typical of someone intent on selling an idea (of little practical use in this case, where the ultimate aim is not to sell a product). A major opportunity thus arises for the country, with scope for training - for example - expert patients, well versed in health matters and DTx, who can be seen as the most credible and balanced healthcare system stakeholders to explain not only what these approaches can offer, but also what should not (or cannot) be expected of them. Very useful input in this process of awareness raising/training can be offered by doctors or other professionals with inside knowledge of the organizations that engage in clinical testing and use of DTx, or with experience of their use, or with (inter)national standing as reference points for the DTx sector and its practical application.

In organizational and economic terms, critical issues must be addressed when the decision is made to adopt DTx, with the need to identify appropriate pathways for their use and to ensure systematic implementation of organizational units that can provide support for the healthcare professionals and patients using them. The following actions thus become necessary:

1. clarify whether DTx are being used as a replacement for, in addition to or in association with drugs, medical devices and technologies, etc.;

2. define whether DTx are part of a care pathway (CP) or a network organization (possibly of a hub and spoke type), which will have implications for decision-making, for their delivery and monitoring, as well as in terms of who is responsible for their efficacy;

3. identify benefits in terms of appropriateness and level of cover for potential health needs (e.g., for patients spread out over an extensive catchment area, or living in relatively inaccessible places), as well as efficacy and cost-effectiveness in relation to the patient/treatment/outcome;

4. identify the various types of costs: direct and indirect; accountable and non-accountable; quantifiable, or related solely to potential inconvenience or risk for the patient, applying the cost-benefit categories applied in Health Technology Assessment (HTA) evaluation. In this case, models and techniques must be adapted to the specificities of DTx, as distinct from the approach used for drugs, medical devices and other technologies;

5. identify patients' and caregivers' digital barriers in relation to use of DTx (from internet connection to availability of devices and appropriate skills).

With regard to the cost-effectiveness of DTx, it could be very useful to devise more agile, leaner systems for promoting collaboration between the public sector and Patients' Associations (e.g., by revision and simplification of the Public Procurement Code and the Code of the Third Sector, with specific reference to Article 55), which should as far as possible be on a uniform basis - or, at least, harmonized - nationwide. To the same end, it would be beneficial to focus on incentives for, and case studies of, successful collaboration between digital start-ups and big pharma, since relations have in many cases proved far from idyllic.

Finally, it is essential to have a clear definition of the decision-making processes involving the patient, the doctor or healthcare professional overseeing the treatment, health board administrators, the leadership of the public or private sector organization, regional or national policy-makers, and the regulatory authority or other body responsible for defining reimbursement arrangements. Generally, in assessing the usefulness of DTx, the use of real life data or patient-reported outcomes or experiences is strongly recommended. In this way, various types of economic assessment could show that DTx, perhaps more than other therapies, enable win-win solutions for all the actors involved. It is also, of course, fundamental that the readiness to use these technologies should

be endorsed by those with formal decision-making powers. For example, in the case of a therapy that has been approved or authorized by a regulatory authority in a country where DTx are not reimbursable by the national health system or by private healthcare/providence/insurance schemes, the decision rests essentially on the will of the prescribing doctor and the patient's readiness to pay. In a country where private reimbursement arrangements are in place, use of a DTx product will depend on the prescribing doctor's willingness to choose this treatment in preference to others, and the decision of the reimbursing organization. In a setting like that of the Italian SSN, the possibility of introducing DTx into clinical practice will depend not only on the regulatory authority, but on the inclusion of the treatments concerned in the Essential Care Levels (in Italy, LEA) lists, budget availability of public or accredited health boards, or patients' willingness to undertake the treatment on an out-of-pocket basis or through private healthcare arrangements. Where reimbursement is available from private schemes or the national health service, it is necessary to identify in which therapeutic classes DTx are categorized. Even in cases where no third party is involved as the source of payment, it is important that the patient should receive a treatment that has been adequately assessed by the authority concerned and fulfils clear value for money criteria.

The question of eligibility for reimbursement is crucial, given the very real risk that even promising technological innovation can unintentionally lead to widening of the gap between rich and poor. For DTx, it is essential not to compound the difficulties that already hinder the achievement of ideal health outcomes for minorities, for fragile subjects, and for the less affluent. In other words, the trend to be avoided at all costs is what some authors have termed "digital disadvantage for the disadvantaged"[6].

These issues must be addressed through strategic planning of digital health interventions, based on the following elements:

- recruitment of diversified subjects throughout the R&D process, in order to allow a thorough assessment of responses and mitigate preferential access for certain population groups;
- understanding of potential end-users' differing social backgrounds;
- participatory user-centred planning, reflecting users' needs and preferences;
- prior assessment of the technological infrastructure needed to allow individual and community use.

3. Conclusions

The **potential capacity** of DTx is an alternative to existing therapeutic approaches (based, for example, on drugs, medical devices or a direct doctor-patient relationship). This could make the public and private sectors alike more willing to invest in innovative R&D, even in sectors where innovation and a return on investment are harder to achieve. This means that instead of the classic financial indicators, it could be useful to leverage parameters like social return on investment (SROI), basing the approach to measurement and accounting on a broader concept of value that can reduce inequalities, increase well-being and reward sustainability by including social, economic and environmental parameters in the cost-benefit analysis.

This is a phenomenon that can mark a shift in companies' strategic choices, allowing health systems to revisit currently available tools with a view to guaranteeing adequate levels of public healthcare. The health agenda of European countries like Italy must therefore prioritize inclusion of DTx in the range of technologies available to the citizen/patient, *inter alia* in light of the resulting investment opportunities and the proven importance of digital solutions for sustainable management of national health services. In this scenario, particularly - as is often the case - at the beginning, it will be important to incentivize and integrate the contribution of private enterprise alongside the role of the public sector, thus favouring development of new evidence for gradual introduction of DTx into clinical practice.

The system cannot afford to allow the same to happen as occurred with CAR-T (a burgeoning innovative sector in oncology today, though the first in vivo experiments actually go back almost a decade), which suffered from an excessively long lead time, with delays in the development of a setting conducive to use of innovative technology and its effective recognition among available healthcare solutions.

For this reason, the fundamental cornerstone for developing DTx in Italy and ensuring their widespread adoption will be implementation of initiatives for creation of a correct scientific, legislative and healthcare framework, together with creation of an adequate educational, participatory and economic environment. To this end, Italy must look at the international and European scenario, particularly Germany, which in 2019 passed a Digital Healthcare Act: since this legislation includes categories of digital health products among those that can be prescribed and reimbursed by the health system, its adoption makes Germany a front runner in extending its reimbursement policy to DTx.

What is known

- DTx could be a new opportunity for a country like Italy to enhance sustainability of its national health service, and thus provide a valid alternative to existing therapeutic solutions and procedures that are, to a greater or lesser degree, innovative
- DTx are a potential incentive to invest in therapeutic areas little explored by industry
- The DTx sector, in Europe and in Italy, can count on an industrial setting conducive to its development
- Europe is backing the development of digital health, enabling investment both in R&D and in strategic upgrading of the system through the Next Generation EU programme.

What is uncertain

- Absence of institutional vision regarding the future of digital health in Italy
- Little or no direct involvement of the healthcare world (even through Scientific Societies and Expert Patients) in the development of new products
- Uncertainty regarding dissemination of the first DTx, already identified as efficacious and approved in other countries
- Lack of an adequate regulatory framework, and of clarity regarding the pathway that these technologies will have to follow with a view to their integration in the available healthcare armamentarium.

What we recommend

- We recommend the identification of institutions, pathways and processes that can give appropriate recognition to the role of DTx within the national health service and favour access to them by properly defined rules and procedures, but also by an appropriate regulatory framework
- Clarity is needed in respect of governance, making it possible to roll out over a period of years a fully fledged and uniform process of digitalization for health services nationwide. In addition, we recommend ongoing dialogue with all stakeholders concerned (companies, universities, the scientific world, Associations and Scientific Societies, patients, citizens, politicians, and relevant healthcare institutions at national and European level), so as to favour the adoption and use of DTx in Italy.

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Digital therapeutics like pharmaceuticals?

1. Digitalization in healthcare

Over the past ten years or so, the digital revolution has radically transformed all sectors of society and, more recently, is starting to produce an impact mainly in the healthcare sector. Two fundamental factors are responsible for this trend, which is nothing short of a revolution: i) the quantity of health data generated by each individual patient; and ii) increased computing capacity, in terms both of storage and of analysis. Against this background, not only are the time and space coordinates of the very concepts of health and disease undergoing a profound transformation, but there are also enormous changes to patients' behaviour and to diagnosis and treatment pathways(1). According to the Observatory for Digital Innovation in Healthcare, Italy showed a 7% increase in turnover for digital procedures in the health field in 2018, bringing the annual total to almost €1.4 billion(2).

By the term "digital health", or eHealth, is meant the use of various digital technologies to support and deliver health services for improvement of individuals' health and well-being, often involving people who are

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not actually ill. The broad category of digital health includes many different technologies, among them telemedicine, social media, applications (apps), wearable devices, smartphones and digital therapeutics (DTx). These technologies present new opportunities for addressing challenges that are on the rise worldwide, the aim being to improve the quality of health services by putting in place a system of patient-centred care[3]. This sector has not yet acquired its own standard vocabulary, but there are three macro-definitions into which the technologies used in the health sector can be bracketed: digital health, digital medicine and DTx. The general definition of digital health includes technologies such as apps or web apps that support users in changing their lifestyle and pursuing goals related to their well-being, generating health data that can, in turn, support research activities and clinical practice. Digital medicine, on the other hand, encompasses a category of clinical evidence-based digital technologies, able to carry out interventions in favour of human health. Finally, the DTx category comprises all those digital technologies that offer evidence-based therapeutic interventions in order to prevent, manage or treat a medical problem or disease[3].

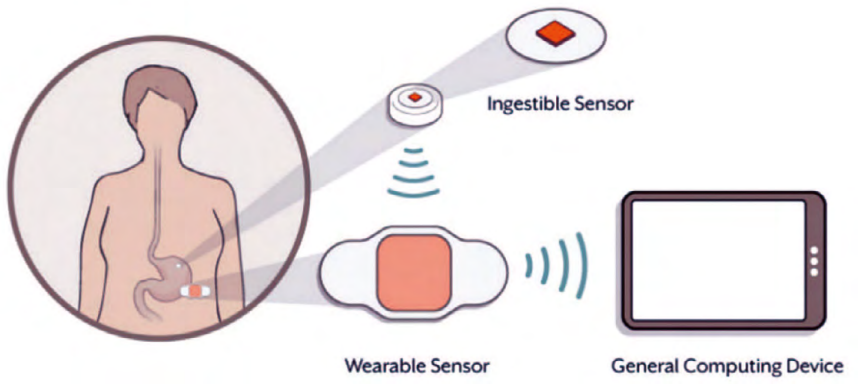
2. The role of digitalization in pharmacological treatment

Most technological applications used by patients are digital versions of so-called Patient Support Programmes (PSP). These tend to be related to organizational or other needs, aiming to give patients support so that they can better manage their illness, understand their overall condition and/or receive counselling on their illness trajectory. Digital PSP are mainly personalized apps, used to promote patient compliance, enhance communication between patients and healthcare providers, offer tools for disease monitoring and, more generally, promote patients' engagement in their own day-to-day healthcare. Considering their capacity to collect data by means of clinical diaries and/or questionnaires, PSP can also be useful for research, obviously in compliance with data protection measures. As applications without therapeutic activity, they are only rarely subject to experimental clinical studies[3].

Unlike PSP, digital medicines are pharmaceutical products in which the drug to be taken is integrated by activation of a sensor after swallowing, the ultimate aim being to guarantee patient compliance. Pharmaceuti-

cal nanotechnologies are no longer surrounded by an aura of mystery, and have entered the market for swallowable treatments. These tiny transmitter sensors can be formulated within a capsule or during manufacture of a tablet; once they reach the stomach, thanks to its acid pH, they become activated and transmit information about the digestive process to which they are exposed, thus affording insight into digestive tract function and absorption of the active principle with which they are associated. This would be confined to the realms of mere technological curiosity were it not for the fact that, in late 2017, the Food and Drug Administration (FDA) approved the first product combined with this type of sensor[4]. Known by its brand name of Abilify MyCite, the product was developed by the Japanese pharmaceutical company Otsuka (manufacturers of the antipsychotic aripiprazole, or ®Abilify) in collaboration with Proteus Digital Health. With the patient's consent, once the sensor has been swallowed it communicates with a stick-on wearable receiver similar to a band-aid; from there, information is then passed on to the patient's (or somebody else's) smartphone or tablet. The final aim is to measure patient compliance in adults with primary psychoses such as schizophrenia, manic episodes or mixed episodes in bipolar type 1 affective syndromes *(Figure 1)*. However, this technology has not proved very popular, resulting in major revenue losses for the company that developed it; probable reasons for this failure are the notoriously uncompliant target patient population, some critical issues such as the view that the patient's psyche is downgraded to the status of a digital dataset[5], or the fact that the need for a stick-on wearable receiver

Figure 1 - Operating mechanism of swallowable sensors[7]



is dismissed as technologically unacceptable in a Bluetooth world. On 17 July 2020, Otsuka withdrew the application for market approval filed with the European Medicines Agency[6].

Another example of digital medicine is the Propeller technology, developed for patients with asthma or chronic obstructive pulmonary disease (COPD). In this case, the sensor is applied directly to the inhaler and automatically registers where, when and how often the drug is used. This information is then relayed to an app on a smartphone[8]. Approved for marketing on 7 July 2020, Propeller is the first such sensor to be authorized in Europe.

Though bracketed by regulatory classification in the medical devices category, the R&D and delivery characteristics of DTx are comparable to those of drugs. Unlike PSP and digital medicines, DTx products are developed by controlled clinical investigation, are subject to a regulatory approval process for specific indications, and are reimbursable and prescribable. What differentiates DTx from a conventional drug is the active principle, which is no longer a chemical or biological entity, but comprises algorithms and software. Like conventional drugs, DTx products too have excipients, such as modules for patient gratification, reminders to take the DTx and complementary treatments, as well as modules for patient contact with the GP and with other patients treated for the same indication. Within the panorama of digital health technologies, DTx are an independent category of evidence-based products whose principal function is to deliver therapeutic interventions generated by software, so as to prevent, manage or treat a disorder or disease[9]. DTx can incorporate additional functions, to enable integration with health platforms, assessment of patient compliance, and combination with sensors or wearable devices. In addition, personalized treatment pathways can be generated, thus optimizing management of the condition according to the individual patient's exact characteristics and bringing so-called personalized medicine up to date in terms of digital technology[10].

DTx can generate therapeutic interventions both on a stand-alone basis and in combination with conventional drugs, integrating software- and algorithm-based technological innovation with drug treatment. Stand-alone DTx products work autonomously, being designed as interventions able to change a patient's dysfunctional behaviours and, in this way, substituting drug treatment. An example of this stand-alone use can be found in psychotherapy of insomnia, depression or attention deficit hyperactivity disorder (ADHD) and schizophrenia, where the development of soft-

ware simulating cognitive behavioural therapy (CBT) models or psychoeducational models has improved patients' clinical outcomes, enabling their direct engagement in disease management[10]. The combination of DTx with conventional drugs, known as augment or add-on treatment, can mean that the two work together to improve the associated drug treatment's clinical efficacy, safety and patient compliance. On the other hand, combination or combo therapy means that the combination of drug and DTx is devised as such from the clinical development phase, which aims to demonstrate the combination's superiority over use of the drug alone[11].

DTx are a new opportunity, mainly for the treatment of chronic disease related to lifestyle and dysfunctional behaviours, where conventional therapy proves only partly effective. DTx can correct these dysfunctional behaviours, stimulating the patient's involvement and active participation, and providing information and support in disease management. For this reason, DTx are particularly suited to deliver treatments that are normally provided in face-to-face encounters, such as CBT and clinical hypnotherapy. The indications for DTx approved to date are for mental disease, metabolic diseases and dependencies. Delivery of DTx by digital devices can offer a number of advantages, such as: (i) easier access to treatment, including during leisure time and not limited to face-to-face meetings with the psychotherapist; (ii) personalization of treatment, on the basis of outcomes and progress observed; (iii) consistent quality of DTx, by comparison with the extremely variable quality of face-to-face treatment with a psychotherapist.

3. Regulatory agencies and DTx

The first DTx product approved by the FDA in 2017 was reSET®, an app developed by the Pear Therapeutics company, followed in 2018 by reSET-O®. Both reSET and reSET-O are examples of prescription DTx, indicated respectively for treatment of substance use disorder and opioid dependence. These treatments are delivered by apps for mobile devices that use a form of CBT known as the community reinforcement approach (CRA), originally developed for alcohol and cocaine dependence.

In June 2020, the FDA approved EndeavourRx, manufactured by Akili Therapeutics, the first game-based DTx device for attention enhancement in children with ADHD. EndeavourRx is indicated for patients from 8 to

12 years with ADHD, as part of a programme that can include clinical treatment, medication and educational programmes[12]. EndeavourRx is based on Akili Selective Stimulus Management (SSME™), a technology designed for targeted activation of specific neuronal circuits, and thus for treatment of diseases with associated cognitive dysfunctions.

Somryst™ is a DTx product approved in 2020 by the FDA for treatment of chronic insomnia, using CBT interventions (CBT-I) in line with the American Academy of Sleep Medicine guidelines as the first-line treatment for chronic insomnia[13]. Somryst™ also provides information on the progression of insomnia, thanks to monitoring of treatment by the physician and healthcare staff on a dashboard that collects data on sleep metrics, clinical parameters like Insomnia Severity Index (ISI) score, and assessments of the patient's quality of life through the Patient Health Questionnaire 8 (PHQ-8).

Oleena™ is the first DTx product developed for oncological indications, approved by the FDA in 2019[14]. It is a PDT mobile app, designed to help oncological patients manage their symptoms and to enable remote monitoring by the medical team. Oleena™ provides personalized recommendations for symptom management, thanks to evidence-based algorithms. This therapy requires the patient's cooperation with the healthcare provider, since the device is initially configured by the latter on the basis of the patient's clinical status, after which the patient will log directly on Oleena™ any symptoms experienced in association with their oncological condition.

In the United Kingdom, before Brexit the National Institute for Health and Care Excellence (NICE) had already set up a working group under the guidance of the National Health Service, to help companies and regulatory boards identify what type of evidence is most relevant to the assessment of digital tools, thus meeting both the NHS' and the patients' needs with a view to accelerating regulatory processes[15]. This initiative is now obviously no longer situated in a European Union context. To date, three DTx products have been recommended for use by NICE, but not yet approved: Deprexis, an interactive medical device with an online base to accompany treatment of patients with unipolar depression or depressive mood disorders[16]; Space from Depression, another online programme for treatment of depression, to be used under a therapist's supervision as an alternative to conventional CBT[17]; and BDD-NET, an online programme for treatment of moderate to severe forms of body dysmorphic disorder[18].

To date no prescribed DTx product is authorized in most European countries. In Europe, the regulatory system for DTx is still immature and there are

no specific regulations for their assessment, or to guarantee their safety and the integrity of the data collected. The European and US regulatory classification of DTx includes them under the heading of medical devices[19-21].

With a view to market approval, a regulatory framework for these therapies is needed, with appropriate distinguishing features from health and well-being apps. Since DTx differ from health and well-being apps in that they can determine a therapeutic effect, for a product to be part of this class evidence of its efficacy and safety must be provided before market approval. This raises the need to establish a regulatory framework for the various types of DTx, with a view to determining what clinical investigations, and how many, are required for purposes of market approval.

4. Critical issues

Despite their documented advantages, DTx present some critical issues. Since the technology involved is still in the development phase, it is not always easy to carry out clinical investigation able to generate sufficient evidence on safety and clinical efficacy. The digital endpoints used in clinical trials for DTx are different from those of traditional clinical trials, and their validation is made difficult by the absence of a gold standard. In addition, the technical characteristics of DTx could be rapidly updated during the course of the trial, and the technology itself could become obsolete even before the trial is over. These therapies must therefore be subjected to rigorous clinical investigation within a very limited time frame, to enable timely generation of robust scientific evidence[22].

The lack of specific regulations to guarantee the safety of these devices and the quality of the data collected is a further obstacle for the development of DTx. Post-marketing surveillance of efficacy and safety, particularly with regard to possible adverse effects like addictive potential or pseudo-specificity of the therapy itself, is therefore a fundamental activity that will have an increasingly important role with the growing uptake of DTx into clinical practice[3]. More generally, the safety of these technologies is a particularly important consideration. In the STARS-ADHD clinical trial, 6.7% of subjects treated for ADHD with AKL-T01 (Endeavour) showed adverse events, in comparison with 1.8% of patients treated with an active control[23]. Overall, adverse events recorded in studies on Endeavour involved 9.3% of patients. These included frustration, headache,

emotional reactions, vertigo, nausea and aggressiveness[24].

In addition, digitalization of health and of the health system calls for greater patient education and engagement, promoting self-management and active involvement in the related decision-making; this process, however, has to be personalized and structured. Excessive patient empowerment could have a negative impact on the relationship with the physician: although these technologies can enable continuous dialogue between medical staff and the patient, there is the risk that unrestrained use of technology can lessen the need for a direct relationship with the specialist and, even more, with the GP.

Another critical issue associated with the use of these technologies, and specifically with wearable devices, is the management and sharing of patient data. Though the digitalization of healthcare is progressing slowly, the quantity of data that can be used for the patient has greatly increased in the last decade, making it necessary to guarantee patients' data protection and security with a view to supporting correct dissemination of DTx[25]. In the United States, management of data obtained by medical devices is regulated by the Health Insurance Portability and Accountability Act, which makes patient consent mandatory for collection and sharing of data. However, data obtained by these devices can be shared in encrypted and aggregate form, without an explicit agreement as to who will have access to the data. In the European Union, the new General Data Protection Regulation (GDPR) does not distinguish between the various forms of digital device, but covers all data generated by wearable devices or health and well-being apps. In addition, the EU requires clearly defined aims for data use, together with patient consent for their re-use and dissemination; patient consent can be withdrawn at any time.

5. Future prospects

Given the growing digitalization of the health world, with an expected market turnover for DTx alone of about $9.4 billion by 2025[26], there is increasing interest in regulatory questions and R&D processes in relation to these technologies. The economic growth of the DTx sector could in future equal, or even exceed, that of conventional drugs, thus enabling greater access to patient-reported real-world data. In the last few years, a lot of pharmaceutical companies have started to cooperate with technology companies for development of DTx. This collaboration brings important opportunities

for development and innovation. The increase in the quantity of data related to every feature of treatment and of the patient/user, along with the availability of increasingly refined statistical predictive systems, could conceivably usher in greater personalization of medical treatment and more thorough assessment of efficacy and safety, both for these treatments and for any drugs associated with them. It should also be noted that combined use of these treatments and of conventional drugs, with the same indication but a different mechanism of action, can determine summation or synergy in terms of efficacy and tolerability, thus bringing added therapeutic value.

The patient's involvement in health-related decision-making processes and in the management of their own health must, however, not come at the expense of their direct relationship with the physician. A physician who fully appreciates the potential of these additional therapies will continue to play a fundamental role in correct assessment and clinical management of treatment, while admittedly leaving scope for greater independence of the patient. The prescriber will therefore have to educate patients to use these therapies correctly, ensuring not only that self-diagnosis and do-it-yourself treatments are out of the question, but also that more fragile patients do not find themselves having to cope with too great an emotional burden.

What is known

- Digital health offers new opportunities for addressing critical aspects of the health system and improving the quality of what is available, aiming at patient-centred treatment and its personalization
- There is increasing attention, among the medical and scientific community and regulatory authorities, to digitalization in the healthcare sector. This applies particularly to development of fully fledged DTx, and also of digital tools supporting conventional drug treatments, some of which have received regulatory approval and are now on the market
- Though DTx are placed for regulatory purposes in the medical devices category, their R&D and delivery characteristics are comparable to those of drugs. As such, they have to be developed by controlled clinical investigation and go through a regulatory approval process for specific indications, in order to be eligible for reimbursement and available for medical prescription
- DTx are a new therapeutic opportunity, mainly for treatment of some chronic diseases associated with dysfunctional lifestyles and behaviours in which drug treatment alone is only partially effective.

What is uncertain

- In regulatory terms, DTx are classed as medical devices; however, in Europe there is not yet a clearly defined regulatory procedure taking into account the specificities of these therapies, whose development requires more rapid lead times than conventional drugs
- The considerable quantity of sensitive data generated by these technologies raises a number of issues in terms of data use and patients' data protection
- It is not yet clear how post-marketing surveillance of DTx safety can be set up, and which authority must be responsible.

What we recommend

- Any DTx must be integrated into a treatment programme, to be decided by the GP and shared with the patient
- As with traditional drugs, any DTx product's placement on the market must be followed by close reassessment of its risk-benefit profile
- It is essential that there should be global harmonization of development and market approval procedures for DTx.

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The patient, digital health and digital therapeutics

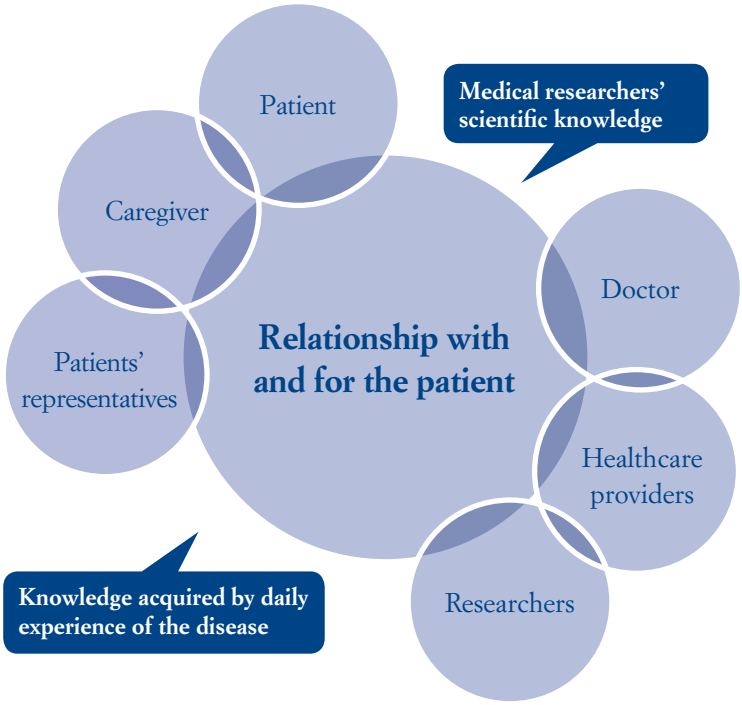
1. Background

In recent years, a new concept of patient-centred care has emerged. Health systems underpinned by value-based medicine and by a lean organizational model presuppose an effort to ensure "value for the patient". As a result, a number of questions arise: Where do we situate, and how do we consider, the patient as part of the system? What do we mean by "value"? Are patients involved in defining what is meant by "value" in health, with the implications this will have for policy and decision-making? Is value to be understood only as that of the patient, or also the caregiver? Which operational tools implement patient value? Can diagnostic and therapeutic care pathways (DTCP) be a major tool for patient engagement? What is the current status regarding these points in Italy?

If "patient value" is indeed a major consideration, the initial approach has to be modified accordingly: the focus must be placed not so much on the patient at the centre of the system as on the caring relationship between the various actors, because it is here that value is produced (as confirmed, *inter alia*, by healthcare litigation data). The patient is just as much a part of the healthcare system as all the other actors, being the main stakeholder in their own health. Alongside the patient, we can find the expert patient (a figure that has emerged in recent years) and the patients' representative. Both these categories collaborate and cooperate with doctors and healthcare providers for continuous enhancement of research, availa-

[1]*European Patients' Academy / EUPATI Non-Profit Organization*
[2]*Italian national Association of People with Rheumatological and Rare Diseases (Associazione Nazionale Persone con Malattie Reumatologiche e Rare - APMARR)*

Figure 1 - The "care relationship" model



bility and delivery of treatments, thus co-generating the "value" of the healthcare supply chain *(Figure 1)*.

Introducing innovative tools to support the relationship among the various actors in the system is the priority: there is a need for "algorithms" connecting the various components and enabling dialogue among the various parties. The "patient" thus becomes the link between health and illness, between scientific and experiential knowledge. The caregiver acquires experience of the disease alongside their loved one, remaining at their side through thick and thin. In most cases, the caregiver becomes the chief support underpinning the patient's life and hopes.

The figure of the caregiver (and the expert caregiver) can in some cases actually take on a leading role, as in the case of partially or totally disabling disease that makes the patient unable to take informed, conscious decisions regarding their own treatment pathway.

Thanks to the rise of empowerment and related social movements in recent decades, patients and caregivers are no longer alone, or passively dependent on decisions taken by others: there are now large numbers of patients' associations that, by their collective effort, have enabled identification of new needs, prioritization of new discussions and creation of new opportunities, thus determining pathways for cooperation with institutions. Patients gain in self-assurance and become accredited interlocutors for doctors, researchers, healthcare providers, administrators and public policy-makers. They become a resource for the health system, able not only to advocate for the needs of the patient community they represent, but also to integrate the patient's perspective into healthcare decisions, to modify healthcare procedures and, last but not least, to play their role in the joint design of their treatment pathway within the broader DTCP roadmap.

In this overall setting of interpersonal relations involving many different parties, the continuum that encompasses information, reception facilities and needs-based care becomes the basis for the relationship of trust between the various actors concerned.

Interpersonal relations can be meant to ensure:

- diagnosis, with the healthcare provider asking the patient the necessary questions. This presupposes that the patient is able to give exhaustive, complete answers;
- concordance between healthcare providers and the patient/caregiver, with a view to optimizing patient care in relation to quality of life and achievement of shared decision-making;
- therapeutic education and adaptation of lifestyle to the patient's new status: this underlines the disease's major impact on the patient's life system, involving as it does their family and social network;
- better quality of life in its terminal phase, with healthcare providers helping to create the best possible care setting in order to reduce suffering and pain.

This means that the relationship between the healthcare provider and the patient/caregiver can have three complementary dimensions:

- cognitive: the healthcare relationship means transfer of information between one component and another;
- technical and gestural: the healthcare relationship enables the patience to learn new techniques, enhancing their know-how;
- emotional-affective-behavioural: this relationship enables the patient

and the caregiver to express their difficulties and their emotional experience, making it possible to identify attitudes requiring specific professional intervention with a view to reinforcement and/or remodulation.

This is where it is particularly important that the healthcare provider should, indeed, "take care of" the patient, with the professional's scientific knowledge offering an opportunity to adapt one's life to major change, within an educational relationship based on significant learning.

Healthcare requires therapeutic education programmes (in other words, secondary and tertiary prevention), based on methodologies underpinned by brain-based activities consistent with underlying needs. Hebb's principle, as described in 1949, postulates that significant, repeated, moving experiences create the basis for increasingly stable cognitive structures[1]. Research in recent decades has highlighted the human brain's plasticity throughout its entire lifespan, since it always remains subject to a series of changes determined by what one learns. These changes can be the basis for enhancement of "intelligence", meaning the capacity to respond effectively and efficiently to given stimuli that have to be interpreted and will then form the basis for decision-making; to trigger action resulting from this; to critically review one's own interpretations and actions; and to adapt them when necessary. Important functions for significant personal learning include attention, planning, results orientation, behavioural organization, strategic thinking, self-control, self-restraint, self-monitoring, and regulation and control of emotions and motivation[2].

To these components of the learning process can now be added the opportunities provided by technological applications. In this sense, digital therapeutics (DTx) can contribute to the daily life of many patients obliged to "learn" a new lifestyle, adapting their daily rhythms and choices to the illness that has become part of their lives. These treatments can achieve a theoretically optimal condition, in that they can support, correct and jointly create cognitive behavioural capacities essential for effective coping and self-care. A fundamental and peculiar feature of DTx is the patient's and/or caregiver's active involvement. This is why, to achieve their full potential, application of these technologies requires a pathway of user profiling and education that must reasonably be part of the clinical practice scenario within which these technologies are implemented.

DTx come into their own in an overall setting within which mobile electronic devices are readily available nationwide. As shown by statistics,

these devices are now almost literally part of our clothing and our accessories: we carry them about with us everywhere. What better instrument to enhance patient compliance and monitor individual health, outside an institutional healthcare setting and as part of our day-to-day life?

If the hardware and the algorithms are now available, the main gap is probably the lack of a strategy for the overall system. Germany, England and France have national digital health policies. An article by Sergio Pillon[3] about application of digital medicine in German healthcare practice, as regulated by a law of 1 January 2020, highlights a number of points that can simplify the patient's and caregiver's life, such as the following:

- apps are medically prescribed once they have passed safety and operational testing. Their use is thus no longer unregulated, but is synonymous with evidence-based practice ensuring full efficacy and safety;
- telemedicine is becoming the norm. Home and clinic are no longer two worlds totally apart, so that the patient and caregiver are no longer obliged to attend clinic and hospital appointments, other than in an emergency and/or for scheduled interventions (examinations, medical checks, etc.);
- digitalization of a patient's medical history makes this a virtual record encompassing disease progression, diagnostic tests, medical reports, etc. Above all, this can be an important tool for reconnaissance and pharmacological reconciliation, because to date there is no readily available summary of the individual patient's different medical prescriptions, other than in cases where patients themselves are meticulous and systematic enough to keep a simple, accessible record of all drugs prescribed and/or taken.

Use of technology can be an asset with a view to promoting patient compliance. Devices dispense treatments and advice, reminding us of when we last took our medicines or have to take them again, showing us how to optimize our lifestyle, displaying our dosage regimen and advising us to consult the doctor when anomalous data are flagged, thus becoming a sort of healthcare watchdog[4]. Digital medicine thus marks a cultural sea change in traditional healthcare: more than the simple adoption of new technologies, it allows delivery of services, supply of materials, participation in experience, accessibility and usability of extensive and varied content, as well as new connections between people, places and things[5].

Digital medicine has a place in many diseases, not always necessarily classified as chronic. It can also be an important asset for patients with ra-

re diseases, currently faced with the fundamental challenge of transitional care. This means making the transition from a paediatric to an adult care setting. The advent of digital medicine is thus a change that can determine quality of life, safety of treatment and, last but not least, patient-caregiver -healthcare provider concordance.

Another aspect that should not be underestimated is enhanced quality of life, not only for the patient but also for family and loved ones, particularly bearing in mind the advantages of better patient compliance, reduced need for care and accompaniment, limitation of journey time to/from clinics and hospitals, and reduction in time off work or in work-related constraints for the patient, and possibly also for family members.

2. Examples of DTx in practice

To offer practical examples illustrating who could benefit from DTx, and how, it is appropriate to look at a number of clinical cases differing not only in patient and caregiver needs, but also in the system of healthcare relations. To provide a representative overview, three cases with different diagnoses have been chosen: a child with autism, an adult with stroke sequelae, and an elderly woman with head injury sequelae.

Common to all three cases is the type of information shared between healthcare and social service staff, patients and caregivers. Classified as sensitive health data, this information refers to the subject's health status; data processing is carried out, in the interest of the subject's health, by healthcare institutions or medical professionals.

As we will see below, data processed for management of these cases comprise:

- diagnostic data (e.g., diagnostic examinations carried out by a specialist, in a hospital department, at a GP's/paediatrician's clinic or pharmacy, or by a physician on house call);
- treatment data: choices of treatment and DTx, with assessment of patient and caregiver compliance;
- rehabilitation protocol data: nowadays, a lot of rehabilitation is done by means of technology at home, with tablets, smartphones and consoles playing an important role in reinforcing messages from professionals such as physiotherapists, speech therapists, etc;

• constant exchange of vital parameter monitoring data. The patient remains at home, while health data are relayed to a telemonitoring station, normally run by hospital staff.

Certain features are common to all three cases presented below:

• presence of a caregiver/family member;
• need to acquire capacities and skills for coping with life change;
• need to feel as autonomous as possible in day-to-day life;
• presence of a contact person/service for treatment;
• responsibility of health services, with activities integrated into DTCP;
• need for a "reconciled" treatment plan (Italian Ministerial Recommendation 17);
• need for close management of daily life, enabling early warning of signs or symptoms related to possible complications;
• individual patients/caregivers to have their own devices.

5-year-old child

Young parents, Italian father, Peruvian mother. Both very present. Case of autism associated with X-linked genetic disease. Self-sufficient in motor and physical function, is growing well, walks, indeed is hyperactive and moves a great deal. No speech, no verbal expression, only sporadic vocalization. Does not make eye contact with people around him and therefore does not interact with them. Lives in a world of his own. Has no relationship with other children of his age. Relationship with the adult world limited to gestures and touch - e.g., if he is thirsty he goes to the refrigerator, opens it and then puts his hand on a bottle. Incontinent, but feels the need to evacuate; his mother has learned to recognize the accompanying gestures and facial expressions, and takes him to the toilet.

A very lively child, with a lovely smile; very fond of music (the father is a musician). Likes water and would happily stay for hours in the bath or in a swimming pool. Very perceptive and sensitive.

Enormous healthcare burden: need for round-the-clock supervision for everything. For a year, has been doing psychomotricity, speech therapy and a specific treatment pathway for autistic children, with poor results.

Probable need for targeted stimuli and personalized interventions that could at least give him a little more autonomy and, above all, improve his possibility and capacity of communicating with, and relating to, others - both children and adults.

Family profile and areas in which DTx are used

Luca's parents (we have given him an imaginary name here) are very attentive to his health condition. They do everything possible for him, striving to create conditions conducive to his receiving the best care. As parents, they have shown their ability to deal continuously with his needs. They have built up an effective relationship with institutions, both for schooling and for healthcare.
Luca's mother does not work and deals full-time with his education. The father is a musician, often away, but very present in terms of contribution to the child's education. Single income family.
Luca has very good digital literacy: he uses the tablet, mobile phone and computer, not only with dedicated programmes, but also with others such as various electronic games. Watching TV calms him down.

Application of DTx for Luca

- Cognitive behavioural therapy through use of games
- Significant learning support
- Role of communicator or linguistic mediator.

Application of DTx for the parents

- Cognitive behavioural therapy for support in day-to-day life
- Significant learning support
- Constant assessment of the caregiver's stress level and/or possible burnout
- Resources network readily consultable.

Giovanni, 48 years

Fifteen years ago, had a thromboembolic stroke that left him for about two months in a coma; residual left hemiparesis and slight dysarthria. Unmarried, was very active and cultured (qualified architect), but in cognitive terms has developed a marked memory deficit for recent events, an attention deficit and a slowing down of ideomotor function that has gradually worsened in recent years.
On the other hand, the hemiparesis and dysarthria have improved and only slight symptoms remain. This improvement was helped by intensive physiotherapy immediately after the incident.
Over the years, the family have consulted a lot of specialists, particularly neurologists, in search of a miracle cure that could bring his memory back and improve his cognitive problems. This has not really proved helpful for him, but has tended to make his interpersonal relations rather hostile and conflictual. Perhaps there is a need for other, specific forms of care to address his limitations.

Family profile

The parents are very present, but after years of knocking at different doors and undertaking journeys of hope have become resigned. They have consulted large numbers of experts, both medical specialists and healthcare providers, in search of a cure that could "bring back the Giovanni we knew". He has a sister who, while close to her parents in striving to give active support, has a family of her own that she must be with.

The father is retired, while the mother does housework for a family living nearby.

The parents are worried about the present and future:

- Today: how can they leave the house, even to go to the shops round the corner, and leave Giovanni alone?
- Tomorrow: what will happen to Giovanni when they are no longer there?

Application of DTx for Giovanni

- Cognitive behavioural therapy, through games activity and connections to long-term memory
- Significant learning support by application of executive functions.

Application of DTx for the caregiver

- Significant learning support for addressing a variety of day-to-day needs
- Constant assessment of caregiver's stress level and/or possible burnout
- Resources network readily consultable
- Monitoring of Giovanni's movements, health condition and vital parameters (if necessary).

Maria, 75 years

In a fall from her bicycle six months earlier, she suffered concussion, with subdural haematoma. She resumed walking shortly afterwards and is quite self-sufficient in her day-to-day life, except in some circumstances where she needs help and stimuli. Automatic actions that are simply a question of carrying out movements are not problematic - e.g., going upstairs, getting up, sitting down, eating once she has food in front of her, washing once she has a face sponge and soap ready to hand, etc.

For all other situations requiring even limited reasoning, she has difficulties - e.g., sowing on a button, looking for an item of clothing in the right wardrobe and putting it on, tying up her shoelaces, crossing the road, reading a few lines in the paper and repeating what she has just read.

She needs almost continuous supervision and assistance. The family is present but needs to be supported, since they underestimate some aspects of her illness and amplify some aspects of her behaviour without managing to help much.
She has done courses of rehabilitation, but of a non-specific nature. What would be needed is a personalized pathway to develop and gratify the self-sufficiency she shows in some areas, but at the same time helping her to realise what her current condition is and work to improve it.

Family profile
Maria has a son and daughter living with their families not far away. She lives with a carer. At least once a day her children visit her. They would be much more involved if they were able to stay connected with her at all times of day. This is not possible, for two reasons: their mother's functional limitations after the accident; and the cost of the technology and related subscription fees needed to address the mother's condition and the children's needs.

Application of DTx for Maria
- Cognitive behavioural therapy to enhance fine hand movements
- Significant learning support by application of executive functions for better motivation and self-esteem
- Patient compliance, given the need to take different courses of daily medication (>5 different drugs per day)
- Monitoring of vital parameters, given that she has various chronic complaints and is in polytherapy.

Application of DTx for caregivers (carer and/or children)
- Significant learning support to successfully carry out different daily activities
- Constant assessment of the caregiver's stress level and/or possible burnout
- Resources network readily consultable
- Remote monitoring of patient compliance and safety of treatments.

Overall, looking at the clinical application of DTx, the following aspects can be highlighted:

Therapeutic indications (for what):
Which of the patient's needs are addressed by DTx?

In the R&D process leading to new health products, patients' needs and the amount of access they have to technology are often not the same as for the clinicians and researchers who interpret their data and represent them. Effort

should be dedicated to setting up a concrete, real pathway to ensure the patient's engagement in the R&D phase prior to introduction of new DTx.

Such efforts to enhance patient involvement (inter alia in the setting of recently developed research models such as comparative effectiveness research)[6] could make for more effective research, to include such methods as the following:

- identify patient, caregiver and community priorities;
- collect feedback on the relevance and urgency of the priorities thus identified;
- test the usefulness and relevance of the questions asked, and their applicability to the real-world scenario;
- identify outcomes of interest;
- perform a reality check;
- identify the best approaches for selecting and collecting data of interest;
- leverage the motivation generated by participation in an innovation development programme;
- facilitate the involvement of other patients, *inter alia* by means of patient associations.

Doctor's and/or healthcare provider's prescription (who prescribes)

Training of doctors and healthcare providers is currently a priority. Whoever prescribes DTx must have specific digital literacy skills and clinical experience, enabling them to promote patients' use of these technologies and raise awareness on the subject. For some diseases like attention deficit hyperactivity disorder (ADHD), the prescribers of DTx are speech and/or rehabilitation therapists.

There are three fundamental points related to prescription of DTx:

- clinical efficacy and safety;
- data protection and cyber security issues;
- reimbursement policy.

For the patient and/or caregiver (for whom)

DTx can be used both by patients and by caregivers, albeit with different aims, the ultimate goal in both cases being to achieve a better condition of life at a time of major change in terms of everyday self-sufficiency. Patients can benefit from improved compliance with the treatment regimen and prevention of complications, while also finding a source of support to motivation, attention and concentration. For caregivers, DTx can be very useful with a view to countering emotional fatigue and managing critical issues, as well as

in terms of ready access to services and remote monitoring of the patient.

It is particularly important to take into account and thoroughly assess the patient's and caregiver's health literacy and digital skills before prescribing DTx. What can happen to a person who is prescribed DTx if s/he does not understand what type of content these applications handle, or does not have basic digital literacy? Another non-negligible aspect is the setting in which DTx will be used, with regard to facilities in the building (connectivity, Wi-Fi, etc.) and availability of personal devices.

Reconnaissance and reconciliation of DTx (what therapeutic implications)

Just as for pharmacological treatment, DTx too should find a place among the tools that enable sharing of therapies between healthcare providers, patients and caregivers, in line with the indications of Italian Ministerial Recommendation 17 of 2014[7].

Reconnaissance comprises collection of complete and accurate information on the patient and on the medicines s/he is taking, this information being indispensable for purposes of correct prescription. Reconciliation of pharmacological treatment is a formal process that allows clear and thorough identification and understanding of the pharmacological treatment taken to date, together with other information on the patient; this allows the prescribing doctor to carefully assess whether ongoing treatment should be continued, modified, partly discontinued or stopped altogether. Implementing these courses of action helps to promote effective personalization of treatment, optimizing its adaptation to the individual patient's history and needs.

Personalization of DTx raises the need to demonstrate the treatment's efficacy and its consistency with the single patient's needs, once the prescribing doctor or healthcare provider has implemented the treatment. This makes it important to identify specific outcome measures, alongside more general treatment endpoints, thus demonstrating the appropriateness of the personalized regimen and any need for modification.

Informed patients: what we know, what we want to know, and how we want to know it (HOW)

The principle that "time spent in communication between doctor and patient is part of treatment time", unfortunately conspicuous by the absence of its acknowledgment in the current organizational setting of healthcare, is the basis of an effective relationship between the healthcare pro-

vider, patient and caregiver (if present). This dynamic includes not only the doctor, but all the figures actively involved in the overall process from pre- to post-treatment: prevention, diagnosis, treatment, rehabilitation and possibly palliative care. Communicating with the patient to convey information so as to obtain their informed consent is thus treatment time.

The patient must be able to give informed consent to treatment, on the basis of information made available by the doctor/healthcare provider that explains the modalities, characteristics and consequences of the intervention. This makes it necessary to adapt language, *inter alia* by identifying appropriate tools and strategies that make it possible to achieve an acceptable level of awareness. This is especially true of innovative treatments that differ from routine approaches, necessarily involving appliances or devices designed for other uses (e.g., mobile phone, television, tablet, etc.). The patient must be able to understand and accept all the hypothetical complications of the treatment s/he is about to undergo, and this immediately brings into play the right to be correctly informed.

Another sensitive aspect, on which it is appropriate that the patient should be correctly informed, is consent to data processing. In cases like DTx, the data identified are transferred electronically and this makes it even more important to reassure the patient that information will not be used for purposes other than those s/he has authorized.

The main questions to which patients generally want an answer at the time of informed consent to data processing tend to be the following:

- What do you want to know about me?
- How is the information about me used?
- In what format are these data managed (anonymous or identifiable)?
- How, and where, are the data stored?
- Where will you collect the data from: clinical file, questionnaires, exams, tests, devices, etc.?
- Are we sure that decisions taken with regard to my health/illness are based on my data, not somebody else's?
- What happens if a hacker accesses the database where information about me is stored?
- Who guarantees that my data are not being used to "profile" my health/illness status - in other words, that they won't be used by third parties for marketing purposes?

Availability of large quantities of data can be an important factor for the health system, favouring predictable treatment outcomes and the development

of increasingly personalized therapies, etc. Given the potential value to society of the health data now available, there is also a rationale for taking the lead in promoting greater empowerment for citizens and patients with a view to sharing such data - obviously subject to appropriate data protection measures.

3. The EUPATI Expert Patient and the R&D process in relation to new (digital) therapeutics

DTx make up a particularly important subset in the overall context of digital health and digital medicine. Details of their regulatory classification, development and availability for the healthcare system are described extensively in other parts of this booklet.

Availability of DTx able to bring real benefit to patients and health systems, with appropriate guarantees to all stakeholders (patients, healthcare providers, decision-makers, manufacturing companies), presupposes attentive management of the R&D process as the leading priority. From this point of view, an important question is: Who are the experts on the disease? Alongside the clinicians and researchers, patients have relevant expertise and skill because they live with the illness, and caregivers share that experience on a daily basis. Since this experiential knowledge has the same level of dignity as scientific knowledge, it is of fundamental importance to research, diagnosis and treatment. Patients and caregivers have needs that clinicians often do not know about, or whose degree of priority they do not understand from the viewpoint of the person living on a daily basis with the specific condition concerned. For this reason, in adopting a patient-centred model, patients' thinking must be factored into decision-making about their health.

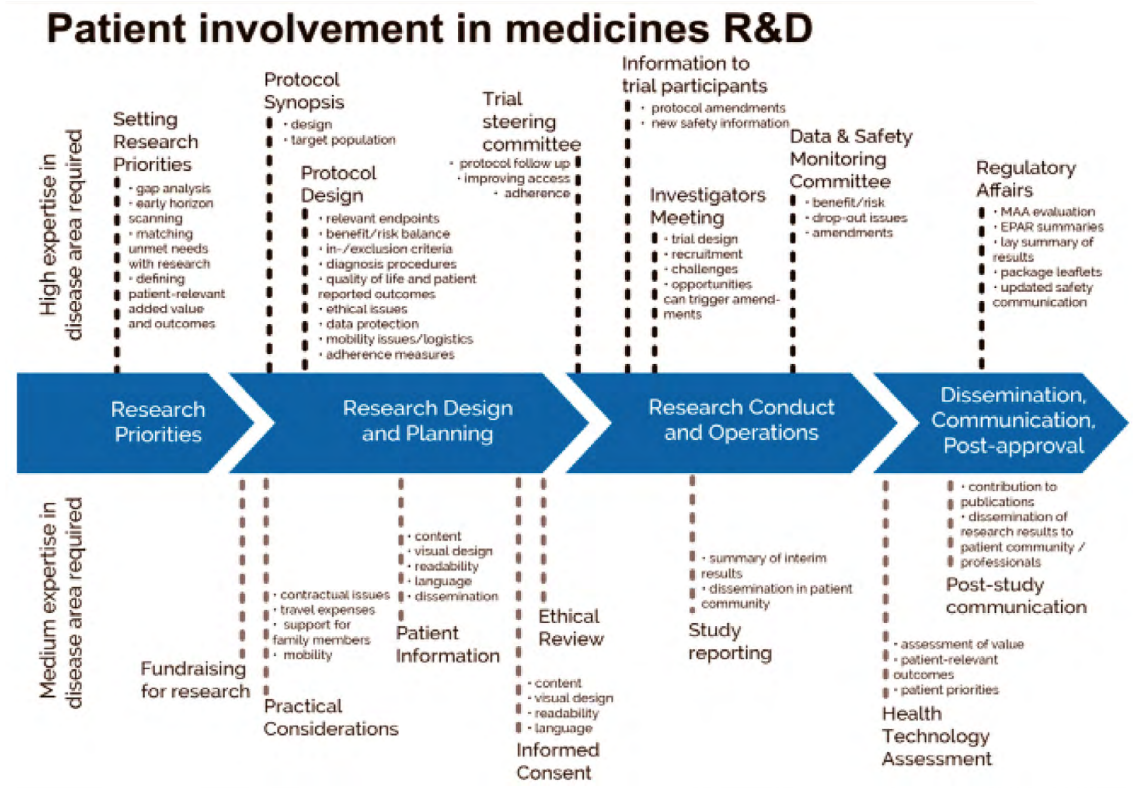
EUPATI (European Patients' Academy on Therapeutic Innovation) is an innovative European project, indeed the only one of its kind, launched in 2012 thanks to input from IMI (Innovative Medicines Initiative). EUPATI involves a consortium of 33 organizations, including patient associations, non-profit organizations, universities and pharmaceutical companies, and is guided by the patients themselves (European Patients Forum). In addition to creating a high-level course for patients on pharmaceutical research and development, which has been successfully completed to date by over 150 Expert Patients from 31 different European countries, the EUPATI project has also developed the online platform "Toolbox". Available in nine different languages, this major platform contains informative materials explaining the A to Z of

pharmaceutical R&D. In recent years, EUPATI has become a certified brand and a synonym for quality in patient training; its input has driven public debate on patient involvement in pharmaceutical R&D. The new Italian offshoot *Accademia del Paziente Esperto EUPATI onlus* recently concluded its first training course, graduating 50 Italian expert patients who will be working together with Italian EUPATI Expert Patients trained at European level.

Figure 2 shows the core curriculum of the EUPATI Expert Patient course, on the basis of which training is devised and dispensed by means of classroom lessons, distance learning modules, webinars and forums (at basic and advanced level).

Despite the specificities of these technologies (extensively discussed in other chapters of this booklet), R&D for DTx has many features in common with validation of new pharmaceuticals, including the potential contribution

Figure 2 - Areas of intervention for patients in the pharmaceutical R&D process[8]



of Expert Patients. Areas of interest here include a number of practical concerns that are fundamental to the patient and caregiver. FAQ in this respect, in addition to those on management of personal data, include the following:

- What does clinical investigation of DTx set out to do?
- Who promotes the investigation?
- Who is my clinical contact person?
- How long does the study last?
- What happens at the end?
- What are the side effects in this specific case?
- What do "screening" and "follow-up" mean in the case of DTx?
- What are the risks and benefits? Are these "safe" treatments?
- What impact can DTx have on quality of life, in relation to the proposed indication?
- Can I withdraw my consent? What happens if I no longer want to take part in the experimental study? What consequences does that have?
- Must I bear any costs (travel, diagnostic tests, drugs, subscription fees, rental deposits, etc.)?

It is in this setting that the Expert Patient takes on an important role: design of a new algorithm must address patients' and caregivers' needs, in the same way as for new molecules. Just as drug R&D involves selection of the most appropriate and user-friendly pharmaceutical forms, for DTx too a system of patient and caregiver engagement is needed in order to set up an interface as closely tailored as possible to the characteristics and needs of the target patients/caregivers.

In an optimal scenario, just as occurs for clinical investigation of drugs, patients should be involved from the very earliest stages of designing the related technology - which means not waiting, as often happens, for the start of pilot clinical testing or usability testing. Asking two or three non-specialists for their comments on the algorithm is not enough. It is also methodologically wrong, just as it is wrong to use a convenience sample for testing an algorithm's usability. Early, structured involvement of patients and caregivers in the R&D process probably enables maximization of the technology's potential efficacy and safety, allowing more appropriate assessment of its characteristics and helping ensure that therapeutic performance will address the patient's most pressing needs.

Looking specifically at DTx, compliance with the criteria and methodological rules of research, with a view to ensuring valid clinical investigation, must be complemented by a number of other considerations that cannot be underestimated at the planning stage:

1. The patient's and caregiver's digital skills: not everyone is a digital native. While age can be a factor in this regard, it is important to be systematic in assessing the digital literacy of the person who will be using the tools (and this also applies to healthcare providers);

2. Availability of devices: just as it is important not to take for granted that all patients and caregivers will have the latest model of smartphone or tablet, it should also be remembered that not everyone will even have one;

3. Internet access: not everyone will have taken out a subscription with a network provider, and this is a point that needs to be thought through. How right is it to "advise" people that they should purchase a subscription with an internet provider? In addition, cover can be patchy in some parts of the country;

4. Deposit for rental of devices: this can be a big outlay for some families. When an app is prescribed and the related hardware is available on a loan for use agreement (the most common arrangement), who has to meet the bill for the deposit fee, or for any repairs and maintenance?

In conclusion, development of DTx applicable to many chronic and other diseases, both widespread and rare, is certainly to be seen as an opportunity for health systems and citizens. In these therapies, the patient's active participation is particularly important - it is, indeed, an essential factor with a view to identifying possible needs and priorities to be addressed by these technologies, and a *sine qua non* for their success. In this respect, it is surely reasonable to propose that patients and/or those who care for them at family/society level should be involved as early as possible in the design and validation of these products. A significant role to this end can be played by figures like Expert Patients, meaning people who have received appropriate and rigorous training that enables them to give effective support in R&D decision-making for healthcare products. In the same way, the importance of the patient's active participation in the treatment pathway presupposes that prescribing DTx should go hand-in-hand with close prior assessment of expected patient compliance, based on effective and informed use of technology.

What is known

- Our point of view as patients and/or caregivers in relation to treatments is generally different from that of healthcare providers
- Our experiential knowledge, enhanced by specific learning that we acquire autonomously or with the help of experts, is integrated with the scientific knowledge of healthcare providers
- Knowledge of our history as patients and/or caregivers is required by

healthcare providers, with a view to implementing the best possible personalized treatment pathway.

What is uncertain

- The rationale for the healthcare provider's decision-making (concept of shared decision-making).

What we recommend

- Shared decision-making based on healthcare provider-patient concordance, with the caregiver's support
- Giving due recognition to the experiential knowledge of the patient as a fully fledged partner in the treatment pathway, including the R&D of new treatment products
- Clear clinical indications for DTx, prescribed by healthcare providers with the necessary expertise and skills
- Integration of DTx into therapeutic reconnaissance and reconciliation processes (e.g., Italian Ministry of Health, Recommendation 17 - 2014)
- Basic digital skills for the healthcare provider
- Patient's and caregiver's level of confidence with DTx to be ascertained.

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Digital therapeutics: ethical aspects

Introduction

Digital technology applied to healthcare offers remarkable opportunities to improve sustainable access to health and deliver better quality of care. This has led to a proliferation of smartphone- and web-based health applications that are changing the ways patients manage their health and interact with physicians. Digital tools to manage health - of which health-re-

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lated apps are a subset - can be situated across a broad spectrum: from non-interventional apps like those designed for fitness, to non-regulated direct-to-consumer apps, to prescription-only tools[1]. This heterogeneous array of continuously emerging technologies, collecting and processing sensitive health-related data, raises a number of specific concerns associated with safety, efficacy, privacy, and accountability. The overarching issue in this regard is that most digital technologies in healthcare do not follow a regulatory pathway; and, in some cases, there may even be a degree of ambiguity in the manufacturer's description of their intended use.

In this chapter we will analyse the ethical concerns relevant to the application and implementation of digital therapeutics (DTx), as a subset of the broader field of "digital health". As stated elsewhere in this book, DTx are medical devices delivering therapeutic interventions, in which a high-quality software application or algorithm constitutes the "active principle". DTx need to be clinically validated through rigorous evidence-based clinical studies (both pilot and pivotal), approved by regulatory authorities, and preferably prescribed by physicians. These characteristics differentiate DTx from most of the other health products that fall under the more general heading of digital health (e.g., wellness apps that can be downloaded from online stores, or others that are available on a smartphone and measure heart rhythm). The implementation of DTx is aimed at: i) making available devices of proven efficacy and safety, to integrate or replace traditional treatments or provide a therapeutic option for a wide range of chronic diseases and clinical conditions; ii) fostering equitable healthcare provision by improving access to effective therapeutic solutions; and iii) empowering patients and caregivers, through their direct engagement in their own care management. However, these undoubtedly promising statements of intent should be adequately nuanced, and their implementation requires thorough ethical evaluation. Indeed, the collection and processing of sensitive health data have reshaped the concepts of privacy and confidentiality, raising the need to address relevant ethical issues that are far broader in scope than the obvious data protection concerns.

Without claiming to be exhaustive, this chapter focuses on ethical issues raised by the implementation of DTx. The aim is to provide a basis for engagement with potential stakeholders, about a critical area of concern within the thorough and wide-ranging evaluation to which this emerging healthcare trend must be subject.

1. Digital therapeutics: a universal and equitable approach

In the challenge of achieving universal health coverage, one of the World Health Organization's greatest commitments, it has become increasingly clear that e-health can potentially play a crucial role. In this respect, implementation of DTx represents an important step towards equitable health service provision, grounded in the fundamental principles of universality, fairness and equity, and in adequate safeguards for the sustainability of national health systems - particularly those characterized by universal access. To be successful, the implementation of DTx in healthcare should take these fundamental principles into account, in both the development and post-marketing phases.

Development phase

The principles of universality, fairness and equity should play a key role in the development process of DTx. Selection bias, with cultural, educational, gender or geographical components, has been reported in the literature on clinical development of drugs and other health technologies[2]. The concerns thus raised also apply to DTx development, and must be addressed in order to ensure that controlled experimental settings are as consistent as possible with real-world conditions. In addition, ensuring fairness in the development phase means that DTx and the underpinning algorithms cannot be allowed to replicate - or, even worse, exacerbate - health inequities. Examples of development phase bias feeding into such inequities are melanoma detection applications trained only on white skin, or algorithms that delay lung cancer diagnosis or underestimate need for extra care in patients of low socio-economic status[3].

DTx should be the output of a co-design process that involves software developers, clinical experts and patients' representatives as partners, while other stakeholders may also be included in specific cases - e.g., representatives of the caregivers or providers who would be in charge of the digital solution's deployment or post-marketing assessment.

Before approval, DTx are subject to strict verification and validation activities, as specified in local regulatory requirements, in order to demonstrate their safety, impact on quality of life, technical and clinical performance, and - last but not least - their clinical benefit. During the post-marketing phase, the DTx owner is subject to procedures that ensure quality control over the software's entire life-cycle.

Greater engagement of patients and/or caregivers in the development phase (optimization of usability, definition of study endpoints, proposal of methods for enhancing adherence to therapy, etc.) is of paramount importance, and potentially of great benefit. The experiential knowledge of patients with respect to their disease can offer a telling contribution to the therapeutic value of DTx (e.g., by making it more user-friendly): this is particularly significant, considering that the therapeutic success of DTx is largely linked to patient empowerment and engagement.

Post-marketing phase

During the post-marketing phase, generation of real-world data is all-important. The implementation of DTx can offer a unique opportunity to promote equitable provision of healthcare, but there are several major factors related to their use that may hinder this positive aspiration. Usability of DTx depends on users (both patients and healthcare professionals) fulfilling a number of specific requirements or preconditions, in terms of infrastructure, tools, financial resources and skills. In order to interact with DTx, the patient needs both a device (not necessarily latest-generation, but certainly not too old) and a stable connection. While in some circumstances the fulfilment of these two requirements may seem a given, in others - especially for those people who would benefit most from the implementation of digital health coverage - this is not the case. These basic needs should therefore be factored into DTx development, dissemination and adoption strategies. The CoViD-19 pandemic, which in many countries has forced the closure of schools and the implementation of distance learning activities, has highlighted how many families still struggle to cope with the digital divide. In the health sector, the need to ensure adequate and widespread remote monitoring for patients with chronic diseases (e.g., diabetes) has in some cases prompted policymakers to make the necessary IT platforms available to patients free of charge. The fulfilment of these requirements depends on financial considerations - both devices and connections come at a price - but also on geographical factors, as there are areas in which a stable connection does not depend on the prospective user's ability to pay. As regards skills, it should be highlighted that the chance to interact with DTx requires a certain level of digital proficiency. Elderly people with reduced mobility are an example of a group that would greatly benefit from the implementation of DTx for better care or improved access to it, but unfortunately they may be short on digital literacy and thus unable to rely on such

support. In this context, the presence of relatives and caregivers may prove fundamental with a view to bridging the digital literacy gap.

Adequate prior assessment of the patient's/caregiver's preparedness and digital proficiency plays a key role - a consideration that should be kept in mind by physicians when deciding whether to prescribe DTx.

Against this backdrop, inclusivity must be prioritized so that otherwise vulnerable user categories are not denied access to DTx. To this end, the DTx functions and interface should be made as intuitive as possible even for inexperienced users. In addition, physicians prescribing the therapy should dedicate time to prospective users and their caregivers (when available), in order to familiarize them with the process. Potential language barriers also require attention: DTx should be made available in a wide range of languages, in order to facilitate user interaction. As a general concept, the language should adapt to the user, and not vice versa. An obvious problem in this regard is that the groups most in need of improved access to care may be illiterate, or speak only minority languages not supported by the system. Finally, there can be barriers related to the availability of devices - and therefore, ultimately, to equity of access: here, the financial burden associated with the use of DTx could be mitigated by making the required equipment available free of charge, or providing reimbursements.

These considerations should play a key role in ensuring that DTx mitigate concerns regarding equity of healthcare provision, rather than exacerbate the digital divide[4].

A critical point is access to these therapies. In theory, DTx - as is the case with drugs - could be used in different ways, from self-prescription to direct payment by the patient, to reimbursement by the national/public health system for DTx prescribed by the physician. Reimbursement policy, obviously applicable only in some health systems, should clearly identify those products that the health authorities have considered to have an adequate - and, if possible, also innovative - therapeutic value. A proper basis can thus be provided for guaranteeing equity and universality of access to this type of therapy.

Finally, we should not forget that, albeit probably to a lesser extent than drugs, DTx are not free from the risk of undesirable effects. As in the case of traditional therapies, careful evaluation of the safety profile associated with DTx is possible thanks to pre-authorization pivotal studies, as well as post-marketing surveillance: the latter makes it possible to obtain information on broader, heterogenous populations, and on long-term safety too. An equally interesting topic is the problem of dropout during clinical studies, or actual

use, of DTx. Close attention to DTx design and user feedback, greater involvement of patients in the development phase and greater user engagement (by such means as emails, texted reminders, etc.) are points that could help reduce dropout rates and therefore optimize the therapeutic value of DTx.

2. Digital therapeutics and patients

The digitalization of health holds intrinsic promise of greater patient education and empowerment, promoting adherence to therapy and active engagement in the healthcare implementation decision-making process. In this perspective, the chance to manage one's own health data with no direct intervention by a healthcare professional is believed to strengthen individual autonomy and enhance the patient's responsibility. However, this begs the question of whether we are sure that this is what patients want. In addition, the promise of empowerment as a result of digitalization has been challenged from different viewpoints that deserve adequate ethical appraisal, with DTx as a case in pojnt. The arguments raised against the promise of empowerment can be broadly divided into two categories:

a. those that recognize empowerment from the implementation of digital health, but highlight possible side effects; and

b. those that challenge the nature of patient empowerment associated with digital health.

According to the first line of argument, while patient empowerment is frequently associated with positive implications, there is a flip side. Patient empowerment has, to some extent, the potential to jeopardize the relationship with the physician. Although the implementation of DTx allows a constant dialogue between clinicians and their patients, there is a risk that excessive reliance on the use of technology may tend to reduce the need for a direct relationship with the physician. In this respect, while the implementation of DTx might play a significant role in the sustainability of the healthcare system, and while the resulting (and admittedly unquantifiable) empowerment of patients has positive implications for their engagement and their care management, both these aspects imply a reframing of the patient-physician relationship. Within this reframing of roles, patients' involvement in management of their own health and in the related decision-making must not come at the expense of dialogue and direct interaction with the treating physician - whose role will, indeed, prove possibly

even more crucial when considered within the overall dynamics and potential of DTx. The role of the physician remains central with a view to ensuring correct evaluation and clinical management of the therapy, albeit with a greater degree of patient independence. Finally, there is the further risk that patients might feel abandoned by their physicians if their reliance on DTx becomes excessive. While a connection between the physician and the patient is still required in the case of DTx, fragile and vulnerable patients might feel that they are missing the benefit of direct, face-to-face interaction with a caring human being.

According to the second line of argument challenging the role of digital health as a source of patient empowerment, the applications concerned - rather than enhancing autonomy - induce patients to comply with a medical regimen by disciplining them and influencing their behaviour. In other words, the reasoning is that individuals using health-monitoring devices are subject to so-called "chilling effects", making them behave in a certain way[5]. According to this viewpoint, the rationale for a certain behaviour is not grounded - as the empowerment-based perspective holds - in the individual motivation to act in a certain way, but in the awareness of being constantly monitored. This prompts the argument that digital health promotes adherence to a certain discipline, rather than encouraging the strengthening of self-determined values[6,7]. An additional critique is that such an approach, rather than strengthening patients' autonomy, assigns them practical tasks (like monitoring symptoms and providing updates) that are generally carried out by physicians and that may entail some stress.

Regardless of the nature and degree of the autonomy promoted by digital tools, the patient's self-management and independence from the physician certainly appear to be greater. Care should therefore be taken to ensure that, rather than slacken interaction with the physician, this patient empowerment associated with DTx becomes an opportunity to strengthen a relationship based on cooperation, with sharing of responsibility and decision-making, so as to achieve better healthcare outcomes. Such an approach makes patients and their caregivers feel that, from the development to the implementation of DTx, their point of view is relevant and their needs are being factored in. Above all, patients' participation provides vital insights into the user's viewpoint. In the long run, this participation and empowerment could positively impact health outcomes, as a sense of engagement should motivate patients to contribute proactively

while also reinforcing their adherence to protocols and therapies. According to this view, empowered patients and their caregivers feel included in the healthcare process. Fostering such a conception of empowerment could provide a basis for a greater sense of the patient's responsibilities, whereby compliance with a medical regimen does not depend merely on their awareness of being monitored by a device.

It will therefore be the task of the prescriber to educate the patient to use these therapies correctly, avoiding self-diagnosis, do-it-yourself treatments and emotional overload for more fragile patients.

A relationship with a software package

Though the essential relationship between patients and physicians must not be relegated to history by the advent of DTx, there is no denying that a major shift in approach is under way. When relying on DTx, the patient interacts mainly with the software. This raises some concerns in terms of professional ethics, since having the therapy managed by an algorithm can potentially disrupt the healthcare provider-patient relationship with the clearly defined obligations that provide a common ground of trust, transparency, and safety between the two[8]. This is particularly true in the context of mental health, where fully autonomous, artificial intelligence-based treatment paradigms are not limited to provision of low-level support (e.g., comfort, social interaction): they also have the potential to carry out high-level therapeutic interventions that are traditionally the exclusive preserve of highly qualified health professionals such as psychoterapists[9,10].

These new approaches potentially contribute to progressive disintermediation[11] between the patient and the physician, increasing the risk of shifting medicine from the "art of curing" to a "science of measurement", where the inner life and feelings of the patient would be forgotten, and interpersonal communication would be secondary to the healthcare provider's informational function[12].

This new scenario requires close observation and study of the implications that transfer of tasks and responsibilities to a software could have, in terms of two important considerations: the perceived role of the doctor, and the feeling of trust that the patient could develop towards the software. In experiencing a sense of independence and self-judgement, the patient could possibly develop a confrontational attitude towards his/her healthcare professional, which would raise the need to rethink medical training or to redirect patient expectations[7].

3. Digital therapeutics: privacy, confidentiality, cybersecurity

DTx, which consist of clinically validated software performing therapeutic functions, are expected to provide a clinical benefit by processing incoming data in order to generate outputs that are able to influence the patient's behaviour. Indeed, the value of DTx is based precisely on the data collected, processed and evaluated (and also possibly used to update/optimize the technology): this applies not only to the pre-authorization phase of evidence-based clinical validation, but - above all - to that of real-world data generation. Hence the need to find a balance between this dynamic and the protection of confidentiality. One variable influencing this balance is the way these therapies are managed - particularly with regard to the doctor's/healthcare professional's role as a guarantor (though the US model is the prime example of a more marked disintermediation in the doctor-patient relationship, with a preference for direct involvement of the technology's manufacturer/developer).

According to the European legal framework, the data managed by DTx are among the so-called special categories of personal data, whose processing is regulated by specific conditions in order to safeguard privacy. Considering the sensitivity of such data, the European General Data Protection Regulation (GDPR) establishes that special categories of personal data shall be processed according to principles of "lawfulness, fairness and transparency"; shall be "collected for specified, explicit and legitimate purposes and not further processed in a manner that is incompatible with those purposes"; shall be "limited to what is necessary in relation to the purposes for which they are processed"; shall be accurate; shall be kept in a "form which permits identification of data subjects for no longer than is necessary for the purposes for which data are processed"; and shall be processed in a "manner that ensures appropriate security of personal data".

Against this backdrop, the focus should be narrowed to the ethical significance and implications of the term "fairness". It is crucial to point out that Article 5 of the GDPR, relating to the general legal principles that have to be respected in data processing, refers in letter a) to the "principle of fairness": by its very nature, this legal principle covers all ethical concerns related to the data processing entailed in DTx.

A relevant source in this regard is the EDPB (European Data Protection Board) document, Guidelines 4/2019 on Article 25 Data Protection by Design and by Default (final draft 20 October 2020). These Guidelines

state that "fairness is an overarching principle which requires that personal data should not be processed in a way that is unjustifiably detrimental, unlawfully discriminatory, unexpected or misleading to the data subject."

Further discussion of the legal framework associated with the processing of special categories of personal data goes beyond the scope of this chapter, but can be found elsewhere in this volume (see Casalicchio E. *et al.*, "Data protection and cybersecurity in digital therapeutics"). What is important from our viewpoint is that the outlined framework serves as a basis for discussing a number of ethical considerations regarding privacy, confidentiality and cybersecurity, in relation to DTx and data processing.

The increasing pace of technological progress, of which DTx provide an excellent example in the healthcare field, has outstripped the traditional conception of privacy. As a simple illustration of this, before the advent of technology as we know it today, any of us could theoretically have felt free to disappear without trace. Nowadays, this would be much more complicated. We are constantly localized and monitored by portable devices[13] that we interact with all day long, providing a ready supply of information related to ourselves. Digital tools know our likes and dislikes on nearly every subject, from political orientation to brands of clothing: they know our habits, our lifestyle choices, and many other traits of our behavior. This raises obvious concerns about the need to ensure that such an abundant source of individual data is used with due care and attention. This is why the implementation of DTx involves a shift in the concepts of privacy and confidentiality. Physicians are no longer the immediate collectors of medical information from patients: devices are. Within this framework, health data collected by DTx constitute sensitive information whose privacy, integrity, and confidentiality require appropriate standards of cybersecurity. The aim is for these data to be protected from unauthorized access or criminal use, phenomena whose incidence is increasing rapidly in the digital world. Once data are collected and processed, they might be stolen, reproduced, and subject to unlimited use. They might also be sold to third parties, for marketing and research. In addition, health records might be used to profile users for advertising purposes[14], or made available on an unauthorized basis to insurance companies as a basis for calculating premiums in relation to health status. Insofar as DTx users have limited awareness and perception of such issues, and of the possible fallout from data breach or piracy, adequate cybersecurity measures should be implemented.

Against this backdrop, the informed consent process associated with

the use of DTx plays a central role in order for prospective users to acquire knowledge regarding the nature and amount of data collected, their possible further use, and the measures put in place to safeguard privacy and confidentiality. Patients relying on DTx need to be properly informed in relation to these points, and should be allowed adequate time to ponder their consent or refusal. Despite the all-important role of informed consent, however, the continuing progress of big data analytics means that establishing clear boundaries is far from straightforward in practice [15]. As Lucivero and Jongsma point out, relying on informed consent is troublesome in a "consumer-focused domain where the mediation of healthcare professionals and researchers is shrinking" [7]. Confidentiality related to health data and records is jeopardized where there is no clear demarcation line between the commercial and medical domains, meaning that online purchases indicative of lifestyle choices can be matched with medical data [7]. Where such a distinction is blurred, there is the need to focus on which data should remain protected, and how.

From this perspective, in order to foster the implementation of DTx, additional efforts should be made to ensure a comprehensive view of the intended and actual use of collected and processed data [7]. Only in this way can preventive measures be set up to safeguard privacy and confidentiality, allowing patients to receive adequate information so that they can make an informed choice regarding the collection and processing of personal data.

4. Digital therapeutics: a reliable pathway

DTx can be seen as exemplary of a reliable and approved pathway by which to realize the benefits of health-related digital technology. Amidst the proliferation of digital tools, the implementation of DTx ideally offers an important, qualified component with a view to delivering sustainable care and improving healthcare access for those in need. The spread of DTx, and their practical relevance to care and assistance, are closely related both to the related clinical benefits and to the regulatory framework.

In order for digital tools to be seen as reliable and widely adopted, users, caregivers and clinicians must be confident of their safety and efficacy, while the tools themselves must obviously earn this trust. Given their therapeutic role, DTx should be developed through appropriate clinical trials that support manufacturers' claims in relation to efficacy, safety and in-

tended use; consistent with this, they must then be subject to a regulatory authorization process for specific therapeutic indications. The prevailing trait of DTx should be the clear and continuous link between the user and the prescribing physician, who is in charge of constantly monitoring the treatment's effects on the user. The certified pathway providing the basis for authorization of DTx is synonymous with accountability for all data collected, while also ensuring the safety and efficacy of delivered care. Certification of this kind is the only way to foster the sustainability of the healthcare system and, at the same time, to effectively deliver better care and improved access to it without exploiting patients' vulnerabilities.

In terms of European Regulations, the key concepts of safety, efficacy, privacy and accountability are described in the two applicable core regulations: the GDPR and the Medical Device Regulation (MDR).

Common to both sets of regulations is a safe-by-design (privacy-by-design) life-cycle approach, in relation to specific international standards (particularly IEC 62304 and the ISO 27000 family). Additionally, the GDPR and MDR have the same approach to accountability, with both stating that the medical device manufacturer is required to appoint a data protection officer and a person responsible for regulatory compliance. The MDR, moreover, requires an evidence-based medicine approach to the efficacy evaluation, specifying that this must be interpreted as clear application of state-of-the-art methods to clinical validation by means of clinical trials.

Overall, the contents covered above highlight how the implementation of DTx requires careful ethical evaluation and adequate education and awareness for clinicians, patients and society at large. Clinicians, who are responsible for prescribing DTx and monitoring their effects, should be formally required to receive adequate digital health training as part of their ongoing professional education: this will enable them to handle related clinical and ethical issues. Patients too stand to benefit greatly from education and awareness. As the spread of direct-to-consumer and unregulated apps becomes increasingly rapid, patients should be properly instructed in regard to the value of their health data, and possible consequences deriving from unintended or unauthorized uses of sensitive items. To this end, patients should be made aware of the differences among digital health tools available on the market - ranging from products of certified providers to unregulated direct-to-consumer apps. This will enable them to make an informed decision in relation to processing of their data. One proposed solution involves the development of labels[16] - like those already used for

foods - to guide users in their choice. Such a system, currently under discussion at regulatory level, would provide an immediate and accessible way to understand the main features of the various digital tools, with a view to comparing them and choosing accordingly.

What is known

- The rapidly emerging use of DTx in healthcare is reshaping the ways of delivering and receiving appropriate therapeutic support. However, these undoubtedly promising trends should be adequately nuanced, and their implementation must be subject to a thorough ethical evaluation.

What is uncertain

- Despite the considerable promise of DTx, the consequences of their clinical implementation are uncertain and deserve appropriate ethical assessment. Relevant concerns in this respect are reliability, safety, privacy, confidentiality, and the physician-patient relationship.

What we recommend

- We recommend active promotion of detailed ethical discussion, starting from the early development stages of DTx. This would provide a sound ethical basis for development of DTx, with timely learning of lessons related to identification of inaccuracies, negative implications, and gaps between intended and actual use.

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Digital therapeutics in General Medicine

Prior considerations

Italy affords an illustrative example of the potential for the use of digital therapeutics (DTx) in the field of General Medicine. Mean life expectancy for the Italian population is currently 80.6 years for men and 85 years for women, with an expected increase of five years for both men and women by 2065, when the forecast life expectancy will be 86.1 years and 90.2 years respectively[(1)]. In 2017, 35% of Italians were over 65 - 5% more than the main figure for Europe as a whole[(2)]. About one elderly person in two suffers from at least one serious chronic disease or is multi-chronic, more than 60% of them being over the age of 80[(3)]. Chronic diseases, which by definition require long-term treatment and multidisciplinary support, currently account for 70-80% of health resources[(4)]. This results in increasing pressure on the health system, against a background of a shrinking and crisis-ridden national economy. Even before the severe economic fall-out from the CoViD-19 pandemic, in 2018 Italy's debt/GDP ratio was as high as 134.8%, higher even than during the Second World War, when it peaked at 118% in 1943[(5)]. The high mean age of national health service staff, with staff turnover deliberately placed on hold as the principal measure for containing the health budget in recent years, is an additional critical factor[(6)].

Against this background, the way healthcare is delivered raises the

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need for careful thought about the advisability of introducing innovative organizational models, based on measurable and predetermined efficiency and sustainability parameters.

In this perspective, future health policies must of necessity prioritize the focus on patient-centred models, underpinned by the concepts of community care, fragility and multidisciplinary integration. There are few points on the health agenda that find such ready consensus as the need to invest in community care, prioritization of primary care, its integration with hospital care (within the overall development and coordination of social and health services), and the need to ensure availability of the tools best suited to this task (above all, digitalization).

Expectations

Technological innovation, particularly with regard to technologies underpinned by analysis and processing of electronic data, has a greater potential than ever before to make this change materially possible.

In this regard, the introduction of DTx within the Italian health system is a new opportunity to provide broadly accessible therapeutic solutions that offer three main advantages: 1) address therapeutic needs that remain unfulfilled by current traditional treatments; 2) offer therapeutic products with a high safety profile; 3) move beyond the "one fits all" approach that is typical of common drug treatments, thanks to the capacity of DTx to generate masses of extremely valuable health data that are specific to each single patient, and to remodulate treatment on the basis of this information.

Emblematic in this respect is the positive impact on home treatment for cancer patients demonstrated by the US Company Voluntis, with the introduction of the DTx product Oleena. The therapy, comprising an app used by the patients for reporting to the oncology clinic any adverse events that have occurred during treatment, makes it possible to follow the clinical course of the patient's condition and intervene as appropriate in relation to the ongoing treatment. Patients have benefited from significantly higher overall survival than those treated on a standard-of-care regimen[7]. On the basis of these data, the app was given FDA certification and will soon be accessible for clinical use by US patients.

Impact on the General Practitioner's professional practice

The Digital Therapeutics Alliance classifies DTx in the following 4 functional categories:

1. management of a clinical condition;
2. management and prevention of a pathological condition;
3. optimization of treatment;
4. treatment of a pathological condition.

The various DTx products that have been approved to date or are currently in advanced clinical development are indicated for many different chronic pathological conditions, such as depression, substance dependency, insomnia, hypertension, obesity, schizophrenia, generalized anxiety disorder, asthma, chronic obstructive pulmonary disease and type 2 diabetes.

Clinical management of these new therapeutic tools is therefore bound to depend first and foremost on primary care, meaning General Practitioners (GPs), paediatricians, clinical specialists, nurses, community healthcare providers and the health authority staff who are the linchpin of care for chronic conditions.

The use of DTx based on input from the GP broadens the armamentarium available to all community healthcare staff, ushering in a new concept of treatment that is proving able to address important clinical needs not fulfilled by traditional care models. Above all, this new approach makes it possible to generate huge quantities of clinical data that enhance knowledge of disease and improve outcomes.

From Big Health Data generated by DTx, artificial intelligence-based systems can offer the GP a dashboard with a comprehensive view of the patient's clinical condition. This further advantage is not an end in itself, but allows the GP to have constantly updated real-life clinical data for the individual patient, leading in turn to personalized decision-making on the basis of predictive outcomes automatically generated by the machine learning software. Important challenges of General Medicine, like clinical monitoring, patient compliance and community care, can thus be addressed. In addition, managing clinical parameters in this way makes it possible to integrate them with data in the electronic patient medical record, today still essentially a bureaucratic concept, thus giving scope for horizontal flows of knowledge and information in General Medicine research. This aspect is also particularly important in relation to the very topical subject of telemedicine, for which many potential clinical ap-

proaches are applicable in actual practice only if the doctor can have an overall view of the patient's health data. In this respect, the customary diagnostic step of asking patients for details of their pharmacological and clinical history becomes particularly complicated in the setting of a teleconsultation with elderly, polypathological and fragile subjects.

All health technologies, before and during use, require regulatory surveillance of their ethical, clinical and social impact on the healthcare system. Digital products are no exception in this respect. The GP can play a leading role in the paradigm shift that we are now experiencing, and need not be seen simply as the user of new tools. In the last 40 years, drug classes that have come to play a fundamental role in primary care (antihypertensives, anti-inflammatories and bronchodilators being just a few examples) have been developed in academic research contexts, coming into contact with community medicine only after they have entered clinical use. This means that the GP has until now been essentially a consumer of new therapeutic products, developing the evidence-based dimension of professional practice in an observational setting. To date, as an example, analysis of Italian General Medicine publications shows a majority of observational studies, almost always centred on organizational aspects of the profession, with very few experimental clinical studies. This means that there is little if any precedent in Italian general medicine for fully fledged, autonomous experimental investigation, able to address GPs' clinical, professional or management issues.

DTx, given their intrinsic characteristics, are developed by digitalized clinical trials with a decentralized set-up, taking place outside the clinical investigation centre. In this type of arrangement, recruitment, data collection and analysis take place close to the patient's natural care setting, so that s/he does not have to go constantly from home to an investigation centre. This arrangement is a significant opportunity for giving new impetus to clinical research in General Medicine. The GP, together with community care providers, is a privileged observer of real-life clinical dynamics, and thus steps naturally into the role of investigator in this innovative form of clinical trials. In addition, the digitalization of clinical research makes it possible to negotiate some of the barriers that have so far slowed down clinical research in General Medicine, particularly in relation to the type of premises required – e.g., mandatory facilities for storage of pharmaceuticals, equipment and instrumentation (refrigerator units, etc.), study data archives (with related data protection requirements).

However, before DTx research and its application in clinical practice can be managed in the community care setting, the GP must acquire full mastery of new treatment concepts such as online consultation and recruitment, digital patient-reported outcomes and biomarkers, wearable medical devices, data protection, machine learning and artificial intelligence. This means that the GP needs to undergo specific training, devised to complement development of clinical expertise with acquisition of skills from other disciplines such as data science. The aim is to prepare doctors and healthcare providers for ongoing or future changes to the healthcare sector, as a result of new technologies coming into use. DTx offer a significant example of this, but not the only one.

Mastery of DTx certainly requires the will to address broad-spectrum scientific challenges, typical of frontier research. As an example, investigation of DTx presupposes definition of digital endpoints without ready availability of a gold standard in the literature. The same is true of assessing the dose-response curve for treatments whose active principle is an algorithm. Even understanding this active principle (algorithm) is technically challenging in the case of machine learning-based algorithms, whose performance can shift in response to acquisition of new training data while the study is still in progress. Though DTx do not exert their main action through metabolic processes, the occurrence of adverse events cannot be ruled out. On the one hand, prolonged exposure to DTx software enables interaction with the subject and positive changes (efficacy) in terms of human behaviour; on the other hand, however, it is important not to overlook the risk that this can induce negative behavioural changes such as dependencies, sleep disorders or postural problems. In the same way, one cannot rule out the possibility of interaction between several DTx products administered at the same time, just as occurs with pharmaceuticals.

Strictly technical considerations of this kind still have to be addressed. They offer the GP who acquires experience in DTx R&D the opportunity to build up technical expertise on a par with that of academic researchers, and to break new ground. This creates scope for high-profile professional recognition of community medicine, with combined experience of clinical practice and research finally becoming a *sine qua non* of primary care. The GP, as a clinician and researcher, thus comes to be seen not as a mere prescriber of drug treatments, but as a major therapeutic asset.

The challenge for Scientific Societies and healthcare institutions is to welcome the advent of DTx in the Italian healthcare system and maximize its potential benefits. The rationale for this is based not only on the related health advantages, as discussed above, but also on the resulting strategic added value for the country's economy. In 2018, the global DTx market was estimated at 1.8 billion dollars, with an expected rise to 7.1 billion dollars by 2025[8], the main areas of development being treatment of obesity, chronic respiratory disease and psychiatric disorders[9]. This indicates the scale on which DTx could bring new opportunities for the country's R&D and manufacturing systems, while also ushering in innovative treatment pathways that could enable significant savings for the health system through a more sustainable approach to today's prohibitive levels of expenditure on chronic medical treatments.

In conclusion, DTX are a valuable treatment tool in the complex scenario of healthcare digitalization, offering a real possibility of enhanced efficacy, safety and effectiveness for biomedical research and for delivery of healthcare services. In this respect, DTx can be seen as an indispensable opportunity - not only, as we have seen above, with a view to addressing major challenges of sustainability for the health system, but also for attracting and boosting investments in national research and manufacturing systems.

What is known

- Increased life expectancy and the growing weight of multiple chronic diseases create ever-increasing pressure on the health system, indicating the need for efficient and sustainable organizational models
- Future health policies must necessarily pay close attention to patient-centred models, underpinned by the concepts of non-hospital treatment, fragility and multidisciplinarity
- In the definition of health investment policies, there is now widespread consensus on the need to promote community care, with a major role for primary care side by side with hospital care, prioritizing development and coordination of health and social services accordingly
- Application of digital technologies to healthcare, including the use of DTx, is a significant opportunity for a boost to the system's efficiency, with the GP taking on a particularly important role in managing progress towards the objectives that this entails.

What is uncertain

- Taking up the opportunities offered by digital health medicine treatment presupposes a major update in terms of technological know-how and cultural approach, still not adequately or uniformly achieved in many countries
- Traditionally, pharmacological treatments for chronic diseases are developed in an academic research setting, but are then mostly used in community care. DTx are predominantly developed by digitalized clinical trials that provide an opportunity for closer involvement of the GP in scientific investigation. To reinforce this, an appropriate regulatory framework and the related infrastructure must be developed accordingly
- DTx can be an option of great interest not only for achievement of healthcare objectives, but also with a view to the health system's sustainability. In some countries (including Italy), it is not yet clear what course will be adopted regarding the place in therapy of DTx.

What we recommend

- For correct and efficient governance of DTx in the community care setting, the GP must be able to understand and manage new concepts of a technological nature, for which adequate training must be organized so the clinical skills can be appropriately complemented
- At institutional level, concrete measures should be taken as soon as possible in terms of regulatory and infrastructure-related needs, so that community medicine and the national health systems as a whole can benefit from the significant potential advantages offered by DTx.

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Digital health, Scientific Societies and Associations of Patients & Family Members

Digital health (DH) comprises the use of information and communication technology (ICT) to treat and educate citizens, carry out research, train healthcare providers, track diseases and monitor public health. DH stands at the crossroads of digital technologies, medicine, healthcare, lifestyle and society, the aim being to ensure more efficient, personalized and precise delivery of treatment.

DH is constantly evolving and growing, the number of medical apps having doubled from 2015 to 2018. The World Health Organization (WHO) decided in 2018 that it was time to set up a classification of DH. The field as a whole was thus broken down into four main areas of interest, based on the targeted primary user and the aim of the intervention[(1)]. The four groups, closely related and interconnected, are as follows:

Interventions for clients: Clients are members of the public who are potential or current users of health services, including health promotion activities. Caregivers of clients receiving health services are also included in this group.

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Interventions for healthcare providers: Healthcare providers are members of the health alliance who directly or indirectly deliver health services.

Interventions for health system or resource managers: Health system and resource managers are involved in the administration and oversight of public health systems. Interventions within this category reflect managerial functions related to supply chain management, health funding and human resource management.

Interventions for data services: This consists of crosscutting functionality to support a wide range of activities related to data collection, management, use and exchange (big data).

From this classification of DH, it is clear that Scientific Societies and Associations of Patients/Family Members can be directly interested and involved in the use, promotion and development of DH.

What Scientific Societies and Associations of Patients & Family Members think and are doing

Analysis of data collected through a web-based search has enabled us to establish that Scientific Societies are generally very interested in DH, even if few of them have issued position statements or guidelines regarding this field.

A 2015 WHO survey of mobile health (mHealth) apps found that about 30% of them deal with diagnosis, treatment and support for mental disorders. Some of these tools have been included in treatment guidelines - in the United Kingdom, for example, two digitalized interventions are recommended for treatment of mental disorders (*Beating the Blues*® for depression; *FearFighter*, for panic and phobia). The World Psychiatric Association (WPA) was among the first Scientific Societies to address the question[2] and issue a position statement on mental health in the digital age, which it calls e-Mental Health (e-MH)[3]. This definition of e-MH applies generally to the overall field of digital technology used in supporting, delivering and improving the mental health and well-being of individuals with psychiatric disorders. Outlining the rationale and potential for using digital systems to treat mental conditions, the document looks at clinical, research, educational and administrative perspectives. The models need to be integrated with traditional practice, to better identify at-risk subjects, awareness and management of mental illness, prevention and early identification of relapses.

Of note, in the field of psychiatric disorders, digital technology can contribute to diagnosis and monitoring, and enhance perception and awareness of disease. A proactive approach is characteristic of e-MH, the aim being to transform the patient's role and experience while integrating different treatments. In addition, as for all DH, there is also the advantage of reducing time and space barriers, particularly in more difficult community settings.

The extent to which technology is used for e-MH, as indeed for DH in general, is evolving very rapidly even if in a spotty and relatively unregulated manner. A recently published meta-analysis of adherence to clinical guidelines examines apps used on iOS and Android platforms, for suicide prevention and suicide risk assessment in patients with depression[4]. Of 69 apps analysed, accounting for a total of 2 million downloads, the analysis shows that 20 (29%) were for management of depression, 3 (4%) for management of depression and suicide prevention, and 46 (67%) for suicide prevention. Only 5 of the 69 apps (7%) offered strategies recommended as the result of evidence-based investigation. In addition, many of the apps in the analysis provided psychiatric emergency contact numbers that were non-existent or wrong. These findings show that manufacturers and app stores have failed to guarantee the necessary quality and safety controls, a trend that should be carefully addressed and that strongly calls for appropriate corrective measures to ensure appropriateness and to avoid commercial distortions.

One of the Scientific Societies that has been most active in addressing the implications of DH is the European Society of Cardiology (ESC), as highlighted by its March 2019 "ESC e-Cardiology Working Group Position Paper: Overcoming challenges in digital health implementation in cardiovascular medicine"[5]. This position paper was developed in collaboration with other Scientific Societies and Associations in the cardiovascular field (European Association of Preventive Cardiology, European Heart Rhythm Association, Heart Failure Association, European Association of Cardiovascular Imaging, Acute Cardiovascular Care Association, European Association of Percutaneous Cardiovascular Interventions, Association of Cardiovascular Nursing and Allied Professions, Council on Hypertension). Essentially, the paper underlines how DH can play an extremely important role in enhancing the quality and accessibility of healthcare for patients with, or at risk of cardiovascular disease.

The ESC's position paper is in line with its mission and strategic plan, one aim of which is to cover all facets of support for the electronic cardiovascular health agenda in Europe. To this end, the paper is intended as a

source of guidance for cardiologists and other stakeholders in the cardiovascular and DH fields. Looking at currently available applications for cardiovascular disease, the document identifies a number of possible challenges to the implementation of DH. One such barrier is the perception among healthcare professionals that heavy time investments are needed to review incoming data and provide patients with feedback: a case in point is the use of telemonitoring programmes for heart failure, which are set up without reducing or adapting the frequency of conventional hospital-based appointments. Further challenges to DH's implementation and development are the paucity of adequate infrastructure and networks, the lack of clearly regulated and standardized procedures, and the need for greater DH expertise and education of healthcare providers.

The American College of Cardiology has also set out a number of principles for support to DH initiatives[6], the main points of which can be summarized as follows:

- enable patient engagement and shared decision-making in care delivery, by providing clinicians and patients with improved access to personalized health information;
- conduct research into appropriate use of DH and its integration into cardiovascular care, to ensure patient safety, care quality and positive health outcomes;
- improve patient experience, care quality, patient safety and outcomes without hampering the clinical workflow;
- foster the development, adoption and evolution of practices that optimize data security, privacy, use and sharing, as well as device security and safety;
- adopt and utilize standardized approaches for seamless data transmission, integration, aggregation and analysis (big data analysis).

In Italy, the Internal Medicine Society FADOI (*Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti*) has always taken an active interest in DH questions, *inter alia* developing an app with diagnostic and therapeutic algorithms for some of the main conditions within the internist's purview (FADOI Guides), and even running an advanced DH course in September 2019 (*Scuola di Alta Formazione sul ragionamento clinico in era digitale*, held in Bologna).

In General Medicine, Italy's *Federazione Italiana dei Medici di Medicina Generale* (FIMMG) dedicated time at its October 2020 National Congress to presentation of a DH survey among the physicians it represents. Respondents' opinions were sought on various aspects of DH, with a view

to subsequent drafting of a position paper. The main findings of the survey can be summarized as follows:

a. digital solutions (apps, use of digital diagnosis and treatment systems) should be "prescribed" and overseen by the doctor, like any other form of diagnosis and treatment;

b. information and data generated by "DH and digital medicine solutions" should be pooled and integrated with healthcare data in General Practitioners's (GP) databases;

c. "DH and digital medicine solutions" are considered by physicians as an opportunity to improve accessibility to health services (with even broader scope at community level, where they are available at the patient's home and GP's office), extending doctor-patient contact and communication;

d. The use of these resources underpins the need for clear, consistent processes, procedures and regulatory frameworks, to guarantee patient safety and ensure that healthcare providers have a full understanding of related medical liability issues. This is also the reasoning behind the recommendation that the solutions proposed should be accredited and subject to adequate and sound certification processes.

Among Patients' Associations, those in the respiratory area were in favour of developing digital medicine technology, confidently expecting significant benefits for the patient's quality of life, particularly in terms of their fundamental right to be treated as far as possible at home.

More generally, a survey of third sector organizations in Italy showed a steady increase since 2016 in the attention and interest prompted by DH opportunities, with scope for development of original and concrete solutions to improve the daily life and health of people with chronic, disabling disease. Projects promoted and supported by Patients' Associations in the last three years have started to be conceived more and more as product-service solutions with a tangible potential impact on the patient's lifestyle and daily life. There is an increasing drive to involve patients and their families in the design and development processes underpinning these new technologies. One of the main aims of Patients' Associations is increasingly to promote, stimulate and support projects and initiatives developed by patients and caregivers, in collaboration with developers and manufacturers, digital technology laboratories and start-ups, pooling the various stakeholders' specific know-how and leveraging the passion they share.

We therefore set out to review experience acquired in Italy, from 2017 to date, with innovative DH solutions involving Patients' Associations and

the patients themselves. This enabled us to identify a total of 150 projects, in each case looking at details of the digital product and/or service concerned. Of the 150 solutions thus identified, about 47% (71/150) include a service component (application, platform); while about 20% (31/150), as pure service solutions, are wholly digital in nature.

Three examples of significant experiences in this setting are:

- DEEBEE.IT YAGI: a tool for monitoring children's blood sugar levels, developed by the diabetes Association of the same name. This is an open computer system for remote, real-time online visualization of values identified by a blood sugar sensor, allowing children with diabetes to attend school safely. Remote monitoring allows the doctor or a family member to track blood sugar levels even on a personal computer, smartphone or smartwatch;
- TASKABILE: a free app that runs on a smartphone or tablet, for persons with intellectual and interpersonal disabilities, developed by the Veneto region chapter of ANGSA (*Associazione Nazionale Genitori Soggetti Autistici*). The aim is to stimulate and facilitate learning of logical sequences, helping to acquire certain skills for everyday life and social interaction. This goes hand in hand with promoting self-sufficiency, making it possible to communicate and execute choices by means of personalized/personalizable categories and images;
- SAFE@HOME: self-sufficient living becomes reality. A prototype house that, thanks to sensors and a cloud platform, makes reports and alerts available to caregivers, healthcare providers and technical/maintenance staff. Guarantees continuity of care and assistance for persons with cognitive deterioration.

Italian digital therapeutics survey (*Terapie Digitali per l'Italia - #DTxITA*)

We ran the survey in July 2020, together with *Fondazione SmithKline* as promoter of the *Terapie Digitali per l'Italia - #DTxITA* project and the FADOI Scientific Society's Clinical Research Department. The aim of the survey, based on a questionnaire for Scientific Societies/Associations and Patients' Associations, was to investigate patients' awareness and experience (if any) of DH activities, together with their opinion of prospects for digital therapeutics (DTx), both generally and with specific reference to Italy.

The questionnaire was completed and returned by 24 Scientific Societies/Associations and 11 Patients' Associations (see list in Appendix), ac-

counting for a response rate of about 40%. Responses received are summarized below, in *Tables 1 and 2*.

Table 1 - Findings from the survey on a group of Italian Scientific Societies and Associations

Questions	answers
Is your Scientific Association/ Society participating in the digital transformation of health and healthcare?	YES 46% NO 42% DON'T KNOW 12%
Has your Scientific Association/ Society promoted initiatives specifically related to digital health/ healthcare?	YES 33% NO 67%
	Type of initiative 40% Training 20% Computer tools for support to the doctor 15% Research 15% Publications 10% Computer tools for support to the patient
Overall, how do you rate what your Association does in relation to the ongoing and expected digital transformation of health/healthcare?	GOOD 21% SUFFICIENT 17% INSUFFICIENT 37% DON'T KNOW 25%
Is there a DH section within your Association?	YES 8% NO, but will be launched by the end of 2020 8% NO 84%
What do you think is the level of awareness in relation to DTx within the specialism represented by your Association?	SUFFICIENT 38% INSUFFICIENT 54% NON-EXISTENT 8%
Do you think that DTx can have a place in the future armamentarium of treatments for your specialism?	YES, with an important role 54% YES, with a marginal role 21% DON'T KNOW 25%
Grade in order of importance (from 1 as the most important to 5 as the least important) these different reasons for which DTx could theoretically be useful in clinical practice:	1. Because they can be an efficacious treatment option 2. Because they can target diseases for which there are significant therapeutic needs 3. Because they can promote more active patient/caregiver involvement 4. Because they can be a safe therapeutic option 5. Because they can save time for healthcare staff

Grade in order of importance (from 1 as the most important to 5 as the least important) these different considerations that could theoretically create limitations for DTx in clinical practice:	1. Many patients might not be able to use them correctly 2. Limited awareness of these therapies among healthcare providers 3. Patient compliance with this type of treatment could be lower that with drugs 4. Could be very time-consuming for healthcare staff 5. Could raise critical issues in terms of data protection and security
Do you think that within the next 12 months the diagnostic and therapeutic guidelines for diseases with which your Association is directly concerned can be updated in line with the development of new digital diagnostics and DTx tools?	YES 38% NO 29% DON'T KNOW 33%
Do you think that Italy can play an important role in DTx R&D?	YES 63% DON'T KNOW 37%
In your opinion, could the introduction of prescribable DTx, reimbursable by the national health service, prove useful for its sustainability?	YES 71% NO 8% DON'T KNOW 21%

Table 2 - Findings from the survey on a group of Italian Patients' Associations

Questions	**Answers**
Is your Association interested in the digital transformation of health and healthcare?	YES 100%
Has your Association promoted initiatives specifically related to digital health/healthcare?	YES 82% NO 18%
	Type of initiative 32% Computer tools for support to the patient 26% Training 16% Research 16% Computer tools for support to the doctor 10% Publications
In your opinion, the overall role of Patients' Associations in relation to the digital evolution of healthcare:	Must be increased 55% Has so far been limited 27% Can be greater than that of scientific associations/societies 9% Has already been significant 9%

What is your overall opinion of your Association's activity in relation to the digital transformation of health/ healthcare?	GOOD SUFFICIENT INSUFFICIENT DON'T KNOW	19% 36% 36% 9%
How do you assess the level of awareness of options known as DTx within the healthcare discipline represented by your Association?	HIGH SUFFICIENT INSUFFICIENT	9% 27% 64%
Do you think that DTx can have a place in the future treatment armamentarium for patients represented by your Association?	YES, with an important role YES, with a marginal role	91% 9%
Grade in order of importance (from 1 as the most important to 5 as the least important) these different reasons for which DTx could theoretically be useful in clinical practice:	1. Because they can promote more active patient/caregiver involvement 2. Because they can target diseases for which there are significant therapeutic needs 3. Because they can be an efficacious treatment option 4. Because they can be a safe therapeutic option 5. Because they can save time for healthcare staff	
Grade in order of importance (from 1 as the most important to 5 as the least important) these different considerations that could theoretically create limitations for DTx in clinical practice:	1. Many patients might not be able to use them correctly 2. Limited awareness of these therapies among healthcare providers 3. Could raise critical issues in terms of data protection and security 4. Patient compliance with this type of treatment could be lower that with drugs 5. Could be very time-consuming for healthcare staff	
Do you think that Italy can play an important role in DTx R&D?	YES DON'T KNOW	82% 18%
In your opinion, the role of the patient/caregiver in technical validation and clinical investigation of DTx could/should be:	Important, but is held back by limited knowledge Important, with the skills already in place to express it Greater than that of healthcare providers	46% 27% 27%
In your opinion, DTx should be:	Usable on a self-prescribed basis or with a prescription, according to the type of DTx Prescribed by the doctor Usable on a self-prescribed basis	55% 36% 9%

Starting from the basic premise that the tendency in this type of survey is usually for respondents to be those with greater awareness and interest in relation to the topic, thus creating a selection bias, Scientific Associations - and, even more so, Patients' Associations - generally show significant interest in DH as a whole and in DTx spcifically. Even if some Associations state that they have already developed specific initiatives in DH, those in the survey recognize overall that awareness and commitment in relation to all these topics has so far been limited. Regarding DTx in particular, Scientific Societies consider that their potential efficacy makes them an interesting option for clinical practice, above all for conditions with major treatment unmet needs and consequent room for improvement; Patients' Associations, in addition to these aspects, underline how important it is to have treatments available that presuppose active involvement of patients and caregivers. Both for healthcare providers' and for Patients' Associations, the main potential limitations of DTx are the inability of many patients to use them correctly and the limited specific know-how among healthcare providers. In all cases, Patients' Associations consider that the patient must have a very important role in initial investigation of DTx. Most Scientific and Patients' Associations are confident that Italy can play an important role in the development of DTx, and that dissemination of this technology can contribute positively to the sustainability of the national health service.

Conclusions

Summing up, the medical and scientific community shows great interest and curiosity in relation to the development, promotion and integration of DH. It is seen as an opportunity not only to treat and educate citizens but also to carry out research, with obvious advantages in terms of acquiring and managing large masses of data, training healthcare providers, tracking diseases, and facilitating patients'/citizens' involvement so as to enhance awareness, promotion of health and management of diseases. With DH becoming an increasingly important part of healthcare, it has enormous potential for development in all its forms and applications. Its promotion could bring extremely important benefits to complex health systems, with ageing populations that suffer from chronic diseases and need frequent reassessments and adjustments of treatment. The spontaneous and disorganized flourishing of DH underlines the need for a well organized playing field with clear regulatory re-

quirements, good coordination and structured contributions, within a health system that fulfils the necessary criteria in terms of know-how, orderly and well-planned integration of hardware/software, etc. In a recent Technology Review Insights survey, run by the Massachusetts Institute of Technology in collaboration with GE Healthcare, more than 900 UK and US healthcare providers saw the application of DH as an advantageous time-saving resource for medical staff, meaning a less crowded schedule for talking to patients and carrying out other procedures. Most respondents also reported that use of artificial intelligence improves the accuracy of predictions and leaves less margin of error in treatment of diseases. These indications are certainly encouraging, but, as already underlined by authoritative sources such as the US National Academy of Medicine, high quality standards must be guaranteed for data, and there must be specific legislative regulation of the DH sector as a whole[7]. In this way, DH should bring a prospect of real benefits not only in strictly clinical terms, but also for health systems as a whole. This makes it necessary to guard against the risk of its piecemeal, unplanned and insufficiently resourced introduction into clinical practice, with a counterproductive effect on the workflow (e.g., lack of a dedicated time slot for analysing remotely transmitted/processed data, thus making further demands on an already full daily workload). Greater control and a regulatory certification process are thus needed, guaranteeing quality and security of access to open platforms for downloads of health-related software that could affect people's health. Actually, without appropriate controls from third parties and regulatory oversight, there is a substantial risk that many new tools will find their way into use mainly for commercial purposes rather than for sound and appropriate evidence-based reasons, with potentially harmful fallout for all the actors involved in the healthcare system chain. DH is an extraordinary opportunity that needs to be overseen and regulated, just as a river is a precious source of water but will often need close monitoring to avoid dangerous flooding when swollen by heavy rainfall.

What is known

- Digital health is a constantly evolving and growing phenomenon
- One of the sectors where digital health has developed most is treatment of mental disorders. However, the rapid evolution of digital health has been accompanied by piecemeal, relatively unregulated availability of technology for medical use, with evidence-based strategies more the exception than the rule

- Given the scale and the sensitive nature of this phenomenon, Scientific Societies and Patients'/Family Members' Associations should be directly involved in the use, promotion and development of technology in the digital health sector
- Even internationally, initiatives by Scientific and Patients' Associations to promote education and research, as well as more extensive awareness raising and analysis, are still rather limited, particularly in the specific sector of digital therapeutics.

What is uncertain

- Promotion of digital health can bring very important benefits to increasingly complex health systems, but it is imperative that the environment should be conducive to this in terms of skills, orderly and well-planned integration of hardware/software, etc
- Outstanding issues include the perception that digital health, without adequate investment and infrastructure, can raise demands on healthcare providers' time because of the increasing information load to manage, with foreseeable implications for the successful use of digital technology in the health field
- Further issues are the availability of adequate, efficient infrastructure and networks, the need for a regulatory framework and standardized procedures, and the importance of promoting digital health awareness and education among healthcare providers.

What we recommend

- To protect all stakeholders, from the patient to the doctor to the healthcare organization, there must be a guarantee that digital technologies applicable to healthcare are adequately regulated and supported by specific legislation
- Associations of Patients/Family Members and Scientific Associations should take on an independent, more active role in fully developing the opportunities afforded by digital technologies
- With specific reference to digital therapeutics, Patients'/Family Members' Associations and Scientific Societies can play an important part in investigating devices, as well as for the necessary awareness raising and training - both for users (patients and caregivers) and for potential prescribers (healthcare providers)
- Italy can play a significant part in the rapidly evolving field of digital

technology for health, and the active role we recommend for Associations should be developed in a timely and coordinated manner.

Appendix

List of patients' associations participating in the "Terapie Digitali per l'Italia - #DTxITA" survey

(The following acronyms are used where applicable: NPO = Non-Profit Organization; 'APS' = Italian acronym for 'Associazione di Promozione Sociale' - i.e., legally recognized Association for Social Support)

- AAI - *Associazione Apnoici Italiani Onlus - APS*
  (Italian Sleep Apnoea Association - NPO / APS)
- AAL - *Associazione Allergici al Lattice*
  (Latex Allergy Association)
- ACTO - *Alleanza contro il Tumore Ovarico*
  (Alliance against Ovarian Tumours)
- ADPMI - *Associazione Diabetici della Provincia di Milano Onlus*
  (Association of Diabetics of the Province of Milan - NPO)
- AIP O.d.V. - *Associazione Immunodeficienze Primitive*
  (Association for Primary Immunodeficiencies)
- AMIP - *Associazione Malati di Ipertensione Polmonare Onlus*
  (Association of Pulmonary Hypertension Patients - NPO)
- ANMAR - *Associazione Nazionale Malati Reumatici Onlus*
  (National Association of Patients with Rheumatic Diseases - NPO)
- APMARR - *Associazione Nazionale Persone con Malattie Reumatologiche e Rare - APS*
  (National Association of Persons with Rheumatological and Rare Diseases - APS)
- *Associazione Italiana Pazienti BPCO Onlus*
  (Italian Association of COPD Patients - NPO)
- FIE - *Federazione Italiana Epilessie*
  (Italian Epilepsy Federation)
- GILS - *Gruppo Italiano Lotta alla Sclerodermia*
  (Italian Group against Systemic Sclerosis)

List of Scientific Societies / Associations participating in the "Terapie Digitali per l'Italia - #DTxITA" survey

(The following acronym is used where applicable: NPO = Non-Profit Organization)

- ACOI - *Associazione Chirurghi Ospedalieri Italiani*
  (Association of Italian Hospital Surgeons)
- AIOM - *Associazione Italiana di Oncologia Medica*
  (Italian Association of Medical Oncology)
- AME - *Associazione Medici Endocrinologi*
  (Association of Endocrinological Specialists)
- CIPOMO - *Collegio Italiano dei Primari Oncologi Medici*
  (Italian College of Directors of Medical Oncology)
- FADOI - *Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti*
  (Federation of Associations of Internal Medicine Clinicians)
- FICOG - Federation Italian Cooperative Oncology Groups
- FIV - *Fondazione Italiana Vascolare Onlus*
  (Italian Vascular Foundation - NPO)
- *Fondazione NIBIT Onlus - Network Italiano per la Bioterapia dei Tumori*
  (NIBIT Foundation - NPO/Italian Network for Tumour Biotherapy)
- *Fondazione Policlinico di Monza*
  (Foundation of the Monza Polyclinic)
- GISCAD - *Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente*
  (Italian Group for Study of Digestive Tract Carcinomas)
- Hunimed - *Istituto Clinico Humanitas* - Humanitas University
  (Humanitas Clinical Institute - Humanitas University)
- IGG - *Gruppo Italiano Tumori Germinali*
  (Italian Germinal Cell Tumour Group)
- IMI - *Intergruppo Melanoma Italiano*
  (Italian Melanoma Joint Group)
- MaNGO Group - Mario Negri Gynecologic Oncology Group
- Meet-Uro - Italian Network for Research in Urologic Oncology
- MITO - Multicenter Italian Trials in Ovarian Cancer

- SIC - *Società Italiana di Chirurgia*
  (Italian Society of Surgery)
- SIDV - *Società Italiana Diagnostica Vascolare*
  (Italian Society of Vascular Diagnostics)
- SIFO - *Società Italiana di Farmacia Ospedaliera e dei Servizi Farmaceutici*
  (Italian Hospital Pharmacy / Pharmaceutical Services Society)
- SIGG - *Società Italiana di Gerontologia e Geriatria*
  (Italian Society of Gerontology and Geriatrics)
- SIGOT - *Società Italiana Geriatria Ospedale e Territorio*
  (Italian Society of Hospital and Community Geriatrics)
- SIMV - *Società Italiana di Medicina Vascolare*
  (Italian Vascular Medicine Society)
- SIP - *Società Italiana di Pediatria*
  (Italian Paediatrics Society)
- SIR - *Società Italiana di Reumatologia*
  (Italian Society of Rheumatology)

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