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

[1] *Smith Kline Foundation, Verona*
[2] *daVinci Digital Therapeutics, Milano*
[3] *Department for Clinical Research "Centro Studi" FADOI (Italian Scientific Society of Internal Medicine), Milano*

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.