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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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