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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.