

Patient-managed digital medical devices: Do we need further regulation?

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ARTICLE INFO

Keywords:

Digital therapeutics
Medical device software (MDSW)
Patient-managed digital medical device (pDMD)
Software as medical device (SaMD)

ABSTRACT

In the heterogeneous category of digital healthcare technologies, software with a medical purpose - i.e. therapy, diagnosis, prevention of a disease or monitoring of adherence to treatment - is expected to have a strong impact. Indeed, it conforms to models of development and market access which are typical of information technology and unusual for healthcare. Avoiding any regulatory uncertainty is crucial for companies and competent authorities. In the European Union (EU), software with a medical purpose qualifies as a medical device, for which a strong regulatory framework is already in place. However, for patient-managed digital medical devices (pDMDs), i.e. software with a medical purpose intended to be used directly by patients, some open issues are still on the ground. These issues arise both at the EU level, related to risk-based classification and clinical evaluation, and the national level, related to prescription and reimbursement policies. The aim of this article is to analyse the classification and regulation of pDMDs in the EU, exploring the need of additional definitions, legislation or guidance.

1. Introduction

Digital and mobile technologies bring the promise to completely reshape the healthcare sector. The process has already started a few decades ago but has more recently grown in complexity and impact, pushed by the marketing success of wearable devices and artificial intelligence. Digital healthcare technologies comprise a wide range of solutions, from telemedicine services to electronic healthcare records, from software driving a hardware medical device to software based on machine learning/artificial intelligence algorithms and used by healthcare professionals in support of medical decisions or directly by patients to prevent or treat a disease.

Software products for digital healthcare may be divided in two broad categories: on the one hand, software with a medical purpose, which includes treating, curing, preventing a disease, or establishing a medical diagnosis [1,2]; on the other hand, software apps for general wellbeing and monitoring of physical activity that do not have a specific medical purpose (not considered further).

According to European Union (EU) legislation, a product which has – or is presented as having – a specific medical purpose is classified as either a medicinal product or a medical device, and it is consequently subject to a strict regulatory framework. Software with a medical purpose is no exception, with the caveat that risk is not related to the

exchange of substances or physical interaction between the body and a device, but to the consequences of indirect effect that can induce the release of endogenous substances or fail to provide correct output during device usage [3]. In particular, in the EU, software intended to be used, alone or in combination, for a specific medical purpose fall under the definition of medical device (MD) or *in vitro* diagnostic medical device (IVD), of which they fulfil the nature (any article, including software), intended purpose and mechanism of action [2]. These devices are named medical device software (MDSW) or MDSW applications (MDSW apps) in EU guidance endorsed by the Medical Device Coordination Group (MDCG) [3–5].

Being a MD or IVD, MDSW should be fully covered by the provisions of the medical device Regulation (MDR) [2] or *in vitro* diagnostic medical device Regulation (IVDR) [6], and not in need of an *ad hoc* regulatory pathway. However, grey areas still exist. This is true, in particular, for a subset of MDSW, that of MDSW intended to be used directly by patients in the treatment, prevention, diagnosis or monitoring of a disease, here referred to as patient-managed digital medical devices (pDMDs).

Starting from the classification of MDSW according to relevant EU regulations and guidelines, this work aims at reviewing the current EU regulatory framework of pDMDs, highlighting open issues and the need of additional guidance and rules, along with a clarification of terminology. Indeed, the growing industrial interest for digital applications in

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Abbreviations	
DTx	Digital Therapeutics
EMA	European Medicines Agency
EU	European Union
HTA	Health Technology Assessment
IVD	<i>in vitro</i> diagnostic medical device
IVDR	<i>in vitro</i> diagnostic medical device Regulation
MD	medical device
MDCG	Medical Device Coordination Group
MDR	medical device Regulation
MDSW	medical device software
pDMD	patient-managed digital medical device
SaMD	Software as medical device.

2. Classification of medical device software

From the point of view of placing on the market, at least two levels of classification should be considered: one based on hardware-software interaction, and one based on the final user.

Based on hardware-software interaction, according to MDCG guidance, MDSW can be classified, as independent or combined. **Independent** MDSW is software with an independent medical intended purpose and claimed clinical benefit, to be run on general-purpose hardware. **Combined** MDSW is software that can achieve its intended purpose only when used in combination with hardware providing input data [3,6,12]. In combined MDSW, the software may be embedded in a hardware MD/IVD, as in the case of software driving a glucose meter, or it may be a MDSW app (not embedded) to be obtained separately and installed on the smartphone or wearable (but also other general purpose hardware), which communicates with an external medical device or which receives data from an incorporated component such as a camera or sensor (Fig. 1).

Moreover, software without its own intended purpose, which drives or influences the use of a medical device may qualify as a component of a hardware MD or an accessory and, while still covered by the MDR or the IVDR, it is not to be considered a MDSW. Examples may be represented by software used to operate a hardware MD, such as graphical interfaces of clinical chemistry analyzers or software informing the operator on the functioning of the device [3,13].

Based on the final user, MDSW can be classified in: MDSW intended to be used by a healthcare professional, and MDSW to be used by a layperson/patient, alone or assisted by healthcare professionals. This classification bears potential consequences on national regulations on pricing and reimbursement policies or healthcare insurance coverage, as MDSW to be used by layperson/patient, unless an integral part of a hardware MD, will pose an issue of market access. Therefore, it is reasonable to single out this category of MDSW, which may be called **patient-managed digital medical devices (pDMDs)** (Fig. 1). The category of pDMDs is largely superimposable with that of German Digitale Gesundheitsanwendungen (DiGA), although not restricted to class I or IIa medical devices [14].

Formally, patient-managed digital medical devices may be defined as MDSW apps, not embedded in a hardware medical device, to be used by a layperson, alone or assisted by a healthcare professional, for a specific medical purpose (in the sense of the MDR or the IVDR). Among the full

the biomedical sector created a new terminology (digital medicine, digital health, digital therapeutics, health apps, healthcare software, medical apps), which is often used improperly, and international efforts towards harmonization have not been fully implemented in the EU [7]. Moreover, in discussing the challenges in qualifying software with a medical intended propose, this work does not include reference to software developed to be used in drug discovery and pre-marketing phases, of which general overviews exist in the literature [8,9] or medicinal products when used in combination with a medical device (including software), already reviewed in a previous paper [10].

A clear classification and nomenclature adopted at the EU level may also facilitate the identification of software categories for which reimbursement policies and/or health insurance coverage may be put in place, helping in the minimization of possible differences between EU countries. Indeed, most pDMDs have been publicly accessible and downloadable from play/app stores worldwide, obliterating the normal “borders” of the European Economic Area. In the Metaverse era, small and unavoidable regulatory differences between different markets may have a strong impact on patients’ awareness on the proper use of pDMDs. A review of current National approaches to the regulation of MDSW can be found in the paper by Essén and co-workers [11].

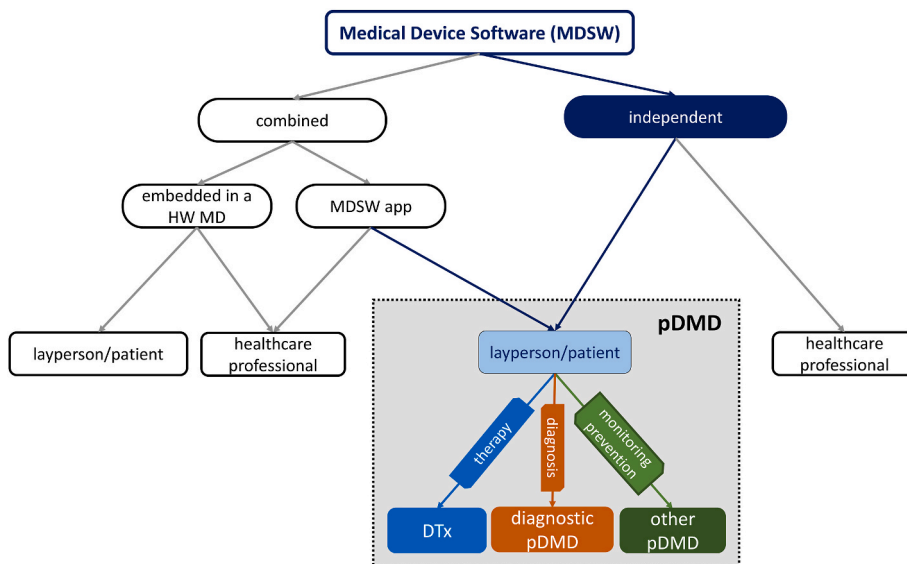


Fig. 1. Proposed classification of medical device software (MDSW). HW = hardware; MD = medical device; DTx = digital therapeutics; pDMD = patient-managed digital medical device.

spectrum of medical intended purposes listed in the MDR and the IVDR, pDMDs marketed until now have been mainly used for therapy, diagnosis, prevention of a disease or monitoring adherence to treatment [8, 15]. When they provide information to be shared with a physician or to trigger a healthier lifestyle (e.g., blood glucose meter software), pDMDs can perform a diagnostic function (although it may lead to a therapeutic decision). Otherwise pDMDs can perform a direct therapeutic function, as in the case video game treatments, in which case they are usually referred to as Digital Therapeutics (DTx), which are defined in the ISO 11147 [16] as “health software intended to treat or alleviate a disease, disorder, condition, or injury by generating and delivering a medical intervention that has a demonstrable positive therapeutic impact on a patient’s health”.

A notable example of an innovative DTx, although marketed in the USA (as a SaMD, software as medical device) and not in the EU, is EndeavorRx®. It is a treatment for attention deficit hyperactivity disorder (ADHD) in children aged 8–12, acting through sensory stimuli and motor challenges. Its safety and efficacy have been demonstrated through 5 clinical studies with over 600 children affected by ADHD [17]. An example of a diagnostic pDMD is a smartwatch app intended to send alarm notifications to the user upon recognizing heartbeat irregularities for detecting cardiac arrhythmia. Examples of diagnostic pDMDs which drive a hardware MD may be represented by the software driving a closed loop insulin delivery system.

On the other hand, MDSW for use by a healthcare professional comprise devices have been designed and manufactured taking into consideration that they are destined to be used by professionals who have been adequately trained in their use and correct interpretation of the results. The therapeutic effect can be direct, as is usually obtained through the control of a hardware MD (e.g., radiotherapy treatment software); or it can be indirect as a result of a diagnostic function, as when software is used either to provide immediate decision-triggering information or support for medical decision (e.g., ECG interpretation software). Example of independent MDSW for use by a healthcare professional is MDSW that uses maternal parameters for evaluating the risk of trisomy 21. One example of a MDSW driving a hardware MD is melanoma image analysis software intended to drive a near-infrared laser light scanner [3].

3. The role of competent authorities

The European Commission, centralized competent Authority for MDs and IVDs at the EU level, has both a legislative function - through the adoption of Commission Regulations - and a coordinating function - mainly through Medical Device Coordination Group (MDCG). The assessment and certification of MDs is left to independent Notified Bodies or, in the case of lower risk devices, to manufacturers. Concerning the European Medicines Agency (EMA), for MD which do not contain medicinal substances, its involvement has always been minimal. However, recently, Regulation (EU) 2022/123 has reinforced EMA’s role in the monitoring of medical devices’ shortages emerged during the COVID-19 pandemic [18]. As an effect, the EMA, through the Executive Steering Group on Shortages of Medical Devices, will work in close cooperation with the MDCG and will provide administrative and technical support to the expert panels established according to the MDR, Art. 106 (1) [10].

At the national level, competent Authorities address market surveillance and reimbursement issues, and the overall picture is fragmented, as different national competent Authorities may be involved in different Member States, and also local regulatory provisions may diverge, particularly concerning pricing and reimbursement.

4. Open issues related to the regulation of pDMDs

Existing EU regulations and guidance on MDs seems to fully cover pDMDs. However, Rule 11 of the MDR classifies in class IIa or above only

software intended to provide information which is used to take decisions with diagnostic or therapeutic purposes or to monitor physiological processes, whereas other software is comprised in class I:

“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” [2].

As it is, Rule 11 seems to prevent pDMDs specifically intended to treat patients, namely DTx, to access higher risk classes, leaving DTx to class I and self-certification for CE marking, which may not be sufficient for software intended to directly treat a disease. A regulatory focus on such products at the EU level is still required.

A second issue concerns the demonstration of efficacy, as clinical evidence gathered to demonstrate the efficacy of MDs for the purpose of CE marking may not be enough for the purpose of Health Technology Assessment (HTA) and access to reimbursement. Moreover, clinical evidence for HTA purposes and for certification purposes is evaluated by different entities. To avoid duplication of data and unnecessary costs for companies, specific regulatory requirements for clinical evaluation should be defined, including the minimum number and nature of clinical trials needed, number of patients, target population. At the national level, procedures for HTA required in the reimbursement negotiation between manufacturers, private healthcare providers and/or national healthcare systems should be defined by each Member State and could take into consideration the evidence already produced for certification purposes.

5. Conclusion

Software intended to treat, prevent, diagnose or monitor a disease is a MD or an IVD, and, as such, within the scope of the MDR/IVDR. However, as highlighted here, existing EU regulations and guidance on MDs do not fully cover the most innovative pDMDs, in particular DTx, such as video game treatments, which apparently are not covered by Rule 11. A first measure that could be considered by the European Commission to clarify the issue would be to revise MDCG 2019-11 to include a focus on pDMDs or DTx.

Moreover, an *ad hoc* term for DTx (or other pDMDs) should be included in the European Medical Device Nomenclature (EMDN). Indeed, most of these products are now destined to enter category “V” (Various medical devices), subcategory “V92” (Medical device software – not included in other classes) [19]. This could represent a first step towards a broader development of legislation on prescription status, HTA and reimbursement at the national level. However, achieving a consensus on definitions, nomenclature and a risk-based classification for MDSW is a prerequisite to be able to address their complexity and heterogeneity.

Aside from manufacturing and certification, the distribution of pDMDs needs to be critically considered, too. It is crucial that patients using pDMDs are adequately trained on their use and have the possibility to reach out to a healthcare professional for guidance and accountability. This could be achieved only if pDMDs are distributed through networks of healthcare professionals - the actual implantation depending on national policies - and are not made publicly accessible or downloadable from play/app stores without the control of a healthcare professional.

Ethical statement

I declare under my responsibility that the manuscript has not been published by any of the Authors, is not under consideration for publication in another journal, its publication is approved by all authors, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright holder.

CRedit authorship contribution statement

Paola Minghetti: Supervision, Conceptualization. **Umberto M. Musazzi:** Writing – review & editing, Conceptualization. **Sara Manelli:** Writing – review & editing, Investigation. **Valentina Pagella:** Investigation. **Paolo Rocco:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Paola Minghetti reports a relationship with Indicon S.r.l. Società Benefit (Italy) that includes: speaking and lecture fees and travel reimbursement. Valentina Pagella reports a relationship with Indicon S.r.l. Società Benefit (Italy) that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Only the Authors have contributed to the manuscript.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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