What medical writers need to know about regulatory approval of mobile health and digital healthcare devices

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Abstract

The rapid growth of mobile health (mHealth) led to the development of internationally harmonised guidance for software as a medical device (SaMD) by the International Medical Device Regulators Forum (IMDRF), covering definitions, risk classification, quality management, and clinical evaluation. The EU Medical Devices Regulation (MDR), applicable from May 26, 2020, onwards, specifically addresses SaMDs and adopted aspects of IMDRF guidance. In particular, Rule 11 of the MDR will have significant implications, as many products so far not classified as medical devices or as class I, may be considered class IIa, IIb, or III medical devices. The entry of technology firms into the medical device field will further drive mHealth and the incorporation of novel technologies into SaMD. This article aims to provide the relevant regulatory background information for medical writers who are requested to support the preparation of the regulatory and clinical documentation for SaMD required for MDR compliance.

The rise of digital healthcare, medical applications, and software as a medical device

The rise of mHealth applications

Digital healthcare (DH) or digital health and care, is defined by the European Commission as tools and services that use information and communication technologies to improve the prevention, diagnosis, treatment, monitoring, and management of health and lifestyle.[1] Central to DH are the three aspects of (1) the DH data input, (2) their subsequent analysis to provide robust and reliable health assessment outputs and (3) the ability for both the input and output information to be transferred between different hardware, often using wireless and mobile networks. The convergence of major technological advances over the last decades supporting all these aspects, as well as societal changes, have led to the ongoing rise of DH aimed to improve access to and quality of healthcare, and increase the overall efficiency of the health sector. Crucial to this is the software that underpins the tools and services that analyse the data to support disease prevention, diagnosis, treatment, monitoring, and management decisions. Accordingly, ensuring the appropriate design and quality of medical software algorithms, as well as ongoing algorithm refinement, including artificial intelligence (AI) and machine learning (ML) software, is key in providing more informed healthcare decisions and improved patient care. Early DH focused on development of digitalised health information systems for patient data management and recording, with DH services like telecare, telehealth, and health analytics for data mining and analysis of health record data, which

were used by trained personnel. Although these products contained software, it was integrated in medical hardware, and thus covered by the applicable medical device regulatory framework. However, in the last decade, mHealth apps, stand-alone software which can be installed on personal mobile phones and tablets, became fully established in DH. From an initial 500 applications available in the first app marketplace in 2008, the field of mHealth expanded dramatically to approximately 150,000 mHealth apps available on the major app marketplaces in 2015,[2] which further doubled to over 300,000 mHealth apps in 2017.[3] Unlike previous DH products, mHealth applications can be developed using platforms with relatively low costs and easily marketed in mobile applications marketplaces. Furthermore, mHealth applications were developed to be used by individuals without medical training, to generate and analyse data and even interconnect with unrestricted body sensors and monitoring devices or wearables.

Development of regulatory frameworks for software as medical devices

To address this rapidly expanding field, the US FDA released a draft guidance on mHealth applications for public comment in 2011.[4] Medical device regulatory authorities of Australia, Brazil, Canada, China, the EU, FDA, and Japan, as well as the WHO, established the International Medical Device Regulators Forum (IMDRF) with the aim to develop a harmonised approach to the regulation for medical devices, particularly stand-alone software. By the end of 2013, the first major mHealth directed regulatory document was released by the IMDRF Software As A Medical Device (SaMD) Working Group, entitled "Software as a Medical Device (SaMD): Key Definitions".[5] According to IMDRF's definition, SaMD (1) must have a medical use of diagnosis, prevention, monitoring, treatment, or alleviation of disease or injury as its intended purpose, (2) does not have to be part of medical hardware, (3) must be unable to drive medical hardware and (4) may be interfaced with, or a module of medical hardware. Subsequently the IMDRF released a guidance document for categorisation of SaMD into four risk groups (I-IV) in 2014,[6] a guidance document on the quality management system (QMS) to be applied to SaMD based on the standards ISO 9001 and ISO 13845 in 2015, and a guidance document for clinical evaluation of SaMD in 2017,[8] all of which were published at the time of the Medical Device Directive (MDD) in the EU. The new EU Medical Device Directive (MDR), will apply as of May 26, 2020, and in addressing SaMD it adopts aspects of the IMDRF approaches with regard to definitions, classification, implementation of lifecycle QMS, and clinical evaluation.[9] This is highlighted in the recently published guidance on qualification and classification of software by the European Commission, which also introduced the term Medical Device Software (MDSW) instead of SaMD.[10] The MDR will have significant implications for mHealth developers to ensure compliance with new requirements. Other global jurisdictions are in the process of adapting their legislation to include SaMD. The primary goals of this legislation are to balance patient safety with timely access to innovative mHealth products, while ensuring the continuous monitoring of the risk and performance profile of mHealth products, with focus on the MDR and personal data protection, including cybersecurity. The aim of this article is to provide an overview of current regulations and standards applicable to mHealth and SaMDs in the EU and US, which are important to know for medical writers who support the preparation of documentation required for regulatory compliance of mHealth products, with focus on the MDR (Table 1).

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Application of the MDR to software and mHealth apps

The extent of required activities for regulatory compliance is based on the risk class of the SaMD. For the manufacturer, the first step in the conformity process for software and apps under the MDR regulation is an assessment of whether the product should be considered as a medical device according to the definitions (Table 2).[9] If this is the case, the second step is to attribute the device to a risk class level based on the classification rules, which will then dictate the requirements for certification.[9] These requirements include a declaration of conformity to the general safety and performance requirements (GSPR), technical documentation, verification, validation, pre-clinical and clinical evaluation, usability, risk management, medical device vigilance reporting, data integrity, information security and, should the conformity assessment

Table 1. Overview of regulations and standards applicable to SaMD in the EU and the US

	Jurisdiction (Regulator)	
	Europe (EU Commission)	US (FDA)
Regulation(s)	• EU MDR 2017/745 • Regulation (EU) 2016/679 (GDPR)	• FDA 21CFR
Standard(s) cited	• ISO 13485 • IEC 62304 • IEC 60601 • IEC 82304-1	• AAMI TIR 45:2012 • GAMP5 – SW Validation
Definitions	• EU MDR 2017/745	• IMDRF/SaMD WG/N10: 2013
(Risk) classification	I, Im, IIa, IIb, III	I, II, III IMDRF/SaMD WG/N12:2014
Product approval	Im, IIa, IIb, III: EC certificate according to MDR issued by EU Notified Body	II, III: FDA approval via PMA or 510k
Certificate validity	Max. 5 years	–
Quality Management System and standards	• ISO 13485 • ISO14971 • EC 62304	• FDA 21 CFR 820 (QSR) • FDA 21 CFR 810 & 830 • FDA 21 CFR 803 • FDA 21 CFR 806
Clinical Evaluation	• ISO 14155 – clinical investigations	• IDE/IRB21 CFR Part 8 • 12, 50, 56, 54, and 820 • IMDRF/SaMD WG/N41:2017
Data protection	Regulation (EU) 2016/679 (GDPR)	• HIPAA • Federal trade commission health breach notification rule

Abbreviations: AAMI TIR = Association for the Advancement of Medical Instrumentation technical information report; CFR = Code of Federal Regulations; EC = European Commission; GAMP5 – SW = Good Automated Manufacturing Practices 5 - Software; GDPR = General Data Protection Regulation; HIPAA = Health Insurance Probability and Accountability Act; IDE: Investigational device exemption; IEC = International Electrotechnical Commission; IRB: Institutional review board; ISO = International Standards Organisation; MDR = Medical Device Regulation; PMA: premarket approval application; QSR = Quality Systems Regulation; SaMD WG: Software as a Medical Device Working Group

Note: Applicable regulations, guidance, and standards are subject to change and it is recommended to always check for current information.

route require it, the involvement of a Notified Body. The medical writer can play an important role in supporting the required documentation, in particular in assessing clinical evidence and the verification and validation of the software with a clinical association. Data sources for mHealth apps include descriptions on mobile marketplaces, in some cases with specific guidelines for medical apps related to privacy, claims, data, and methodology.[11] For SaMD defined in MDR, placement on the EU market is only allowed once it has been demonstrated that the GSPR are met and the product is CE-marked.

Definition of software as a medical device

The governing principle for establishing whether a software or apps is a medical device depends on its intended use (Table 3). If the intended use is for a medical purpose of diagnosis, prevention, monitoring, treatment, alleviation, as well as specific prediction or prognosis of disease and injuries in humans, it is considered as a medical device, irrespective of the type of application. Further, the MDR defines software as an accessory to a medical device if it "enables" or can "assist the medical functionality", which is broader than the corresponding definition in the MDD, that only includes software that "enables" the device as an accessory. In contrast, software and apps used for general lifestyle and well-being software are not considered as a medical device under the MDR, and thus not subject to MDR requirements. According to the MDD,[12] only stand-alone software is considered as a medical device; software embedded or in a medical device does not require certification separate to the device, in line with IMDRF definitions.[5] However, the MDR is not limited only to stand-alone software and states that "devices that incorporate electronic programmable systems, including software" or "devices that incorporate software" must address performance, quality, and risk management procedures.

Classification of software as a medical device

The MDR adopts a risk-based system for classification of stand-alone software from the MDD into four risk classes, considering the degree of invasiveness of the device and taking account the potential risks associated with the devices (Table 3).[12] In addition, the MDR includes a new rule specifically addressing the classification of software. Rule 11 assigns software that provides information to be used for making decisions for diagnosis or treatment to class IIa; however, if these decisions may cause death or an irreversible deterioration of health, or otherwise seriously deteriorate a person's state of health or a surgical intervention, it will be class III or IIb, respectively. Software intended to monitor physiological

Table 2. Definition of software as a medical device according to MDR 2017/745

Software defined as a medical device	**Description**	**MDR ref.**
Stand-alone software	• Software in its own right when specifically intended by the manufacturer to be used alone or in combination, for human beings for specific medical purposes including diagnosis, prevention, monitoring, prediction, prognosis, treatment, or alleviation of disease or injury. • Software used with devices for the control or support of conception.	Recital 19 & Art 2 (1)
Stand-alone software used as an accessory to a medical device	• Software is considered an accessory to a medical device when it is intended by its manufacturer to be used together with one or several particular medical device(s) to specifically enable the medical device(s) to be used in accordance with its/their intended purpose(s) or to specifically and directly assist the medical functionality of the medical device(s) in terms of its/their intended purpose(s).	Art 2 (2)
Software not defined as a medical device	**Description**	**MDR ref.**
Not a medical device	• Not intended to be used alone or in combination for a medical purpose. • Software for general purposes, for lifestyle and well-being purposes is not a medical device.	Recital 19 Art 2 (1)
Embedded software in a medical device	• Devices that incorporate electronic programmable systems, including software, or software that are devices in themselves. • Software that is intended to be used in combination with mobile computing platforms.	Annex I Section 17.1-4
Additional considerations	**Description**	**MDR ref.**
Qualifiers	• Software shall also be deemed to be an active 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.	Recital 19 Art 2 (4)

processes is assigned to class IIa, or class IIb, respectively, if it is used for monitoring of vital parameters, changes of which immediately endanger the patient. All other software not covered by these definitions falls into class I. Software which drives or influences the use of a device shall fall within the same class as the device. The SaMD risk classification has important implications for the manufacturer, as it dictates the conformity requirements. Depending on the manufacturer's decision, multiple conformity routes can be taken for class IIa, IIb, and III SaMDs, which involve assessment by a Notified Body.

Conformity requirements for software as a medical device

The GSPR of the MDR (paragraph 17.1) introduces a new requirement for ensuring software repeatability, reliability, and perfor-mance in line with its intended use and eliminating or reducing as far as possible the risks in the case of a single fault condition. This is coupled with the existing requirements as previously defined in the MDD for development and manufacturing to be in accordance with the state of the art, taking into account the principles of development life cycle, risk management, including information security as well as verification and validation. These requirements are generally addressed by a QMS, thus the implementation of a suitable QMS is a prerequisite for compliance with MDR requirements. Accordingly, international standards like ISO 13485, ISO 14971, and IEC 62304, should be considered in the establishment of a QMS. Notably, the IEC 62304 standard is focused on risk management over the life cycle of the product and on its application to software regulation in the with US, and is closely intertwined with clinical evidence represented by data accumulated on safety and performance of the application through post-marketing monitoring.

Clinical evidence requirements for software as a medical device

The requirements regarding pre-clinical and clinical data for medical devices, including software, are set out in MDR Annex II. Documents outlining clinical data information on tests, generated data, and conclusions demonstrating pre-clinical safety of the software is required. Further, software verification and validation should describe the software design and development process, provide evidence of the validation of the software, and should include testing performed both in-house and in a simulated or actual user environment prior to final release. Presentation of clinical evidence represents an important role for medical writers in supporting conformity assessments. This includes demonstration of a scientifically robust clinical association, validation of the software's ability to generate a clinically meaningful output measure, and critical verification that this output is accurate, reliable, and reproducible. The life cycle requirements set out in IEC 62304 highlight the importance of continuous monitoring, hazard identification and corrective actions as providing a source of clinically relevant evidence that intersects with post-marketing follow-up requirements described in Annex III of the MDR. IEC 62304 recognises the evolving nature of hardware platforms and associated software refinements to both maintain and improve software performance and resulting clinically meaningful measures. By recording, assessing, and integrating data from clinical use into the software algorithms, post-marketing clinical data integrates

into a total product lifecycle approach that is currently advocated by both the FDA and IMDRF.

Promise and challenges on the horizon

Compliance with new regulations

With the impending MDR application, differences in regulations and guidance between the EU, US, and the IMDRF will become more relevant, specifically those related to the broader definition of software as a medical device and risk classification. The MDR requires compliance of medical device manufacturers placing Class I, new, up-classified or modified products on the Market from May 2020, with only limited software-specific guidelines to support developers in their implementation. Because of the risk severity approach combined with the higher rule classification for combined software and medical hardware, many software products will be required to be reclassified into higher risk classes, which imposes more stringent regulatory requirements. In the context of mHealth, compliance to not only MDR but also to the recently enforced General Data Protection Regulation (GDPR) is highly relevant.[13] The GDPR is applicable for companies throughout the world who are processing personal data of people living in the EU and by EU-based companies processing personal data irrespective of whom the personal data belongs to. Anonymisation, when possible, or pseudonymisation of patient data, and its satisfactory encryption must be considered for MDR activities such as post-market surveillance, manipulation, transfer, storage, deletion of clinical data, safety and performance requirements, transparency, and traceability of medical devices. The GDPR imposes much stricter requirements, in terms of data protection, than those in the MDR or the software regulations of the US and IMDRF countries that focus primarily on cybersecurity protection. Compliance with the GDPR is particularly relevant for mHealth apps and will continue to be an important consideration in future software developments.

Artificial intelligence and machine learning-based software as medical devices

AI and ML technologies represent great promise for improving DH and mHealth applications; however, they also raise regulatory concerns, in particular related to their use in medical decision-making. While the MDR does not address AI/ML technologies, the FDA has recently proposed a regulatory framework for modifications of AI/ML-based SaMD for discussion.[14] Importantly, the inherent nature of the constant adaptation of AI/ML software indicates that over time the certified software may become significantly different to when it was initially approved and therefore would warrant a new premarket review to ensure maintained performance and safety. The proposed regulatory framework aims to overcome this issue with a total lifecycle approach, including a closer interaction with developers, identification of pre-determined change types that would be acceptable and periodic update reports on such changes. The FDA has already approved marketing of several AI-based medical devices since 2018.

Entry of technology companies into the medical device market

The entry of the major technology companies into the medical device field by investing in scientific knowledge and partnerships with established healthcare companies and academic labs has the potential to facilitate the integration of new technologies into the healthcare field. Examples of such collaborations, which also engage the user or patient in the development process include Google's Project Baseline[15] and Apple's ResearchKit;[16] or Apple's CareKit,[16] an open source framework to support the development of applications for medical care. Technology companies are also driving integration of mHealth-based apps with wearables, fitness bands, monitors, watches, and rings, to further increase the quantity and quality of available data, but which also raises challenges for MDR and GDPR compliance, as well as cybersecurity and patient's rights.

Table 3. Classification of software as medical device according to MDR 2017/745

Class	Classification criteria	MDR ref. classification rules (Annex VIII)
Class I	• Considered under the MDR as a medical device but not under classification rules as IIa-III	Rule 11
Class IIa	• Informing on diagnostic/ therapeutic decisions, except those which are considered as class IIb and class III • Monitoring physiological processes	Rule 11 Rule 10
Class IIb	• Informing on diagnostic/ therapeutic decisions with impact that may cause serious deterioration of state of health or a surgical intervention • Directly influencing the performance of active therapeutic class IIb device • Monitoring of vital physiological parameters variation of which can cause immediate danger	Rule 9 Rule 10 Rule 11
Class III	• Informing on diagnostic/ therapeutic decisions with impact that may cause death or irreversible deterioration of state of health • For controlling, monitoring, or directly influencing the performance of active implantable devices • With an integrated or incorporated diagnostic function which significantly determines the patient management by the device, such as, are classified as class III	Rule 11 Rule 9 Rule 22
Not a medical device	• Not intended to be used alone or in combination for a specific medical purpose • Data storage or recording only	NA

Conclusions

While mHealth products and the pertaining software have great potential to improve healthcare, their performance according to the claims, and patient safety, need to be ensured. Therefore, international standards for SaMD have been developed by the IMDRF, and regulatory frameworks updated to include software-specific requirements. The MDR, which applies after May 2020 specifically addresses SaMD and will result in up-classification of many mHealth products, imposing more stringent regulatory requirements. Medical writers will play an important role supporting the preparation of regulatory documentation for SaMD required for certification according to MDR. The rapidly evolving technology, including the incorporation of AI/ML and the integration of SaMDs with sensors and monitors will require regular adaptation of regulations and guidance. Stakeholders, in particular SaMD developers, are encouraged to actively monitor development in this field to take necessary actions ensuring compliance with the applicable regulatory framework.

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Conflicts of interest

The author declares no conflicts of interest.

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