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The Challenges of Setting Up a Clinical Study with the New European Union Medical Device Regulation

Os Desafios da Implementação de um Estudo Clínico com o Novo Regulamento de Dispositivos Médicos da União Europeia

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INTRODUCTION

The new European Union Medical Device Regulation (MDR) – Regulation EU 2017/745, which came into effect on May 26, 2021, expands the scope of medical devices to "any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes: diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease; diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability; (…)" (MDR – Article 2),[1] and therefore has had a significant impact in the medical devices industry.

The Apple watch, which analyses heart rate and may potentially detect arrhythmias, was classified as a medical device.[2] Glooko and myDario,[2] which collect and analyze data on a person's diet for the management of diabetes, also received the same classification. Smartphone apps that acquire medical images to enable doctors to diagnose diseases (e.g., pictures of the skin to assess for malignant or benign skin lesions), software that predicts the risk of developing stroke or heart disease, and clinical decision support systems, all became software devices.[2]

According to the new EU MDR, digital health technologies, including apps, stand-alone software, or wearable health devices that claim a medical purpose, qualify as medical devices. Manufacturers now need to provide a clinical evaluation that demonstrates the safety, effectiveness, and benefit of the device (MDR – Article 61),[1] and to go through *conformité européenne* (CE) marking clearance (MDR – Article 10).[1] Moreover, software intended to provide information that is used to make medical decisions qualifies at least as class IIa (MDR – Rule 11 of Annex VIII),[1] which means that it must be assessed by a notified body – an organisation designated by an EU country to assess the conformity of certain medical devices with EU legislation before being placed on the market [MDR – (60)].[1]

Among the changes introduced by the MDR, some aspects pose new challenges in setting up a clinical study with medical software and will be described in the next sections.

CHALLENGES

Understanding the new regulatory requirements

There is currently a lack of clarity regarding how to comply with the multiple new requirements of the MDR.[3] The regulation itself can be difficult to interpret, and therefore templates and guidelines are being developed to support investigators in their submissions to ethics committees and regulators. Documents such as a template for an application to a Medical Research Ethics Committee (MREC) in the Netherlands for non-CE-marked medical devices[4] and the MDCG 2021-6: Regulation (EU) 2017/745 – Questions and Answers regarding clinical investigation by the Medical Devices Coordination Group Document are available.[5] The information is scattered, and each country is producing guidance for their researchers and companies to implement MDR in their setting. Even the authorities are receiving guidance documents, such as the guide for MREC regarding review of clinical research with medical devices.[6] But a concise guide to conduct a clinical evaluation to fulfil a certification procedure is unavailable. Meanwhile, clinical researchers face challenges in complying with the MDR framework and the new rules for the submission of studies, which may complicate and delay the process of conducting a clinical study.

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More documentation and resources to approve clinical studies

The MDR introduces additional requirements regarding the information to be provided to the medical device ethics committee and the regulator for the purpose of a clinical study approval. In addition to a Clinical Evaluation Plan in conformity with the MDR (Annexes IX, XIV and XV),[1] study sponsors need to present extensive documentation of the device, a commercialization label, a complete risk-benefit assessment matrix, and proof of quality procedures through a quality management system (MDR – Chapter II, and Annexes I and II).[1] The device also needs to be registered in the database of EUDAMED (MDR – Chapter III).[1]

Overall, these new requirements make it harder for researchers to navigate the approval process of a clinical study. If any information is missing, additional time is required to obtain it, thus delaying the start of the study. In Europe, it takes a maximum of 60 days for the approval of new studies and 35 days for each amendment (2001/20/EC directive).[7]

This is a particularly challenging period, as standardised protocols are not yet available to everyone. Moreover, compliance of clinical studies with the MDR begins in the early development phases of medical devices. Therefore, the occurrence of a failure to comply with the MDR in the design and development phase, including benchmark testing, could jeopardize the approval for clinical studies with patients and the projects' timeline. The MDR also expects the compliance with the international standard ISO 14155:2020 Clinical investigation of medical devices for human subjects – Good clinical practice[8] (MDR – Annex XV)[1], as well as independent monitoring and auditing for the clinical study (MDR – Annex XV),[1] which entails additional training and human resources. Furthermore, the Clinical Evaluation Report should include both favourable and unfavourable results of the clinical evaluation, as well as reporting of adverse events (MDR – Annex XIV).[1]

More difficulties in finding clinical centers

The EU MDR categorizes medical devices in one of three categories – class I, II (a or b) or III – based on their risk and intended purpose (MDR – Article 51).[1] Clinical evaluation is mandatory, regardless of the risk classification (MDR – Articles 61 and 62).[1] A significant increase in the number of studies with medical devices is expected because under the previous Medical Devices Directive,[9] non-CE-marked technologies in the market were reclassified by the new MDR to a higher risk category that needs reapproval. This means that manufacturers will not be able to produce those medical devices as of May 2024 unless they already generated clinical evidence to fulfil the MDR requirements. Moreover, researchers and companies will have to deal with competition for the same clinical study sites, with inevitable delays. Recruitment time for clinical study volunteers will increase as well, particularly because the number of researchers conducting studies at clinical sites is typically small, and there may not be enough researchers available to conduct the studies at clinical sites. The number of potential participants is also limited, as recruitment usually relies on the researcher's own list of patients. Although these obstacles are not new,[10] the situation may be unprecedentedly critical given the increase in the number of clinical studies.

Higher costs

The new MDR also mandates the subscription of an insurance policy for clinical studies with medical devices (article 69),[1] similar to those of new drugs. Insurance companies assess the clinical study risk mainly based on three factors: the characteristics of the medical device (risk class, CE-mark or not), the stage of the medical device clinical investigation, and the number of patients.[11] Considering the new classification rules for medical devices introduced by the MDR, study sponsors and researchers may face the challenge of a significant increase in study insurance costs. We should stress that the market for insurance companies in Europe is small and not very competitive, which works against researchers and companies. We estimate that the average cost of a study of a class IIa medical device (i.e., most software for clinical decision support systems) should amount to €15 600. If we take into consideration that research on digital and mobile medical devices is mostly undertaken by research units, academia, and small and medium enterprises, we anticipate that the conduct of studies by this sector could be seriously compromised.

Addressing the challenges

Team-based development of medical devices, bringing together engineers, designers, clinical researchers, and regulatory issues specialists seems to be the best approach to meet the demands of a complex regulatory landscape. Early communication with regulatory authorities facilitates compliance with the EU MDR as well. To advance medical devices towards clinical testing, strategic partnerships with clinical sites will play a critical role. On the academic and industry sides, this is the opportunity to ensure the conduct of clinical studies and demonstrate the clinical effectiveness and relevance of their technologies. On the clinical site front, partnerships can bring innovative, breakthrough medical devices to address unmet needs. Implementing decentralized clinical studies by performing remote data acquisition could decrease the burden on staff at clinical sites – one of the main barriers to entering clinical studies – and reduce costs associated with patient visits to the clinic. Finally, research centers would greatly benefit from insurance

companies creating plans for machine learning and mobile device-based studies.

CONCLUSION

Clinical evaluation of medical devices has become a more challenging field, mainly because of the difficulty in complying with the more stringent requirements set out by the new MDR. It is, however, an essential part of innovation and an assurance of safety and clinical benefit for patients. Technology teams must adopt interdisciplinary processes where researchers engage with regulatory authorities during the design and development phases of medical devices. Decentralized clinical studies combined with alliances with clinical sites could potentially secure clinical testing and further regulatory and market approval of medical devices.

AUTHOR CONTRIBUTIONS

SR: Conceptualization, literature search, draft writing and preparation, approval of the final version.

MDM, FN: Review and editing, approval of the final version.

COMPETING INTERESTS

SR and FN are employees of Fraunhofer Portugal AICOS and have received internal funding from this entity.

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