A review of the literature on the new European Medical Device Regulations requirements for increased clinical evaluation

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Abstract

Purpose – The European Union (EU) Medical Device Regulations (MDR) 2017/745 entered into force on May 2021 with changes related to strengthening the clinical evaluation requirements, particularly for high-risk devices. This study aims to investigate the impact of these strengthened requirements on medical device manufacturers by investigating the challenges they encounter while generating an MDR-compliant clinical evaluation report.

Design/methodology/approach – A systematic literature review was carried out using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses method of peer-reviewed literature and various government jurisdictional reports and legislation.

Findings – The findings from the study understanding what constitutes sufficient clinical evidence poses the biggest challenge to the generation of an MDR-compliant clinical evaluation report. Resulting from the challenges they are facing, manufacturers of certain CE-marked medical devices are planning to remove (and have removed) devices from the EU market upon expiration of their certificate, and in the case of new and innovative devices, some manufacturers are planning to launch in other markets ahead of the EU. These challenges will lead to a potential shortage of certain medical devices in the EU and a delay in access to new devices, thereby negatively impacting patients' quality of life.

Practical implications – This study provides a unique insight into the challenges currently experienced by medical device manufacturers as they transition to the MDR clinical evaluation requirements and the subsequent impact on the continued availability of medical devices in the EU. A limitation is the lack of literature analysing the regulations and their effects.

Originality/value – This study has both theoretical contributions in that, to the best of the authors' knowledge, it is the first detailed and systematic review of the new MDR Regulations and has implications for practice as manufacturers and policymakers can leverage it alike to understand the challenges of the new MDR.

Keywords Europe, Systematic literature review, Medical device, Clinical trials, Medical Device Regulations

Paper type Literature review

1. Introduction

Medical devices represent a diverse range of health-care products and technologies designed to improve a person's quality of life (Sorenson and Drummond, 2014). They include simple devices, such as bandages and wheelchairs, to more complex devices such as implantable pacemakers and stents and digital devices, which rely on software, artificial intelligence, the internet and

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wireless technology for enhanced connectivity (Medtech Europe, 2021). Irrespective of the type of medical device or its intended purpose, it must not cause unexpected side effects or serious complications for the end user/patient. Therefore, it is unsurprising that medical devices represent one of the most highly regulated industry sectors (Medtech Europe, 2021).

Before placing a medical device on the European Union (EU) market, the manufacturer must demonstrate to their notified body (NB) that the device is safe for use and performs as intended, or, in other words, that the medical device does not cause unexpected harm to a patient during normal use and functions as expected (Sorenson and Drummond, 2014). A clinical evaluation report (CER) generated by the manufacturer and documents supporting clinical evidence and conclusions regarding device safety and performance are, therefore, one of the key documents submitted to the NB in support of clinical evaluation (CE) marking (Medical Device Coordination Group, 2020). Following an assessment of the CER and other elements of the regulatory submission, if the NB is satisfied that the manufacturer has demonstrated that the medical device is safe for use and performs as intended, the device may be placed on the market. Throughout the lifetime of the medical device, as more information and data are generated from real-world use of the device and collected via the manufacturer's post-market surveillance (PMS) system, the manufacturer is expected to update the CER and other relevant technical documentation.

Before May 2021, European medical devices were regulated under the Medical Device Directive and Active Medical Device Directive (MDD/AIMDD). However, following a series of medical device scandals and in recognition that the directives were not adequate for regulating digital and more complex/sophisticated medical devices, the directives were repealed and replaced by the new EU-Medical Device Regulations (MDR) 2017/745, which came fully into force on 27 May 2021 (Malvehy *et al.*, 2022; Valla, 2021; Deepika Majety *et al.*, 2021). The new regulation is intended to strengthen regulatory scrutiny and oversight throughout the lifetime of the medical device with the overall aim of ensuring patient safety.

According to Holborow (2021), the stricter clinical evaluation requirements introduced by the MDR may pose the greatest hurdle for manufacturers, particularly as the amount and quality of clinical data that will be needed to demonstrate device safety and performance and to support the acceptability of the benefit: risk ratio is set to increase compared to the MDD/AIMDD. Furthermore, given that the NBs' assessment of the manufacturer's CER is subject to scrutiny by the relevant competent authority and, in some cases, by expert panels, manufacturers may experience delays in their product reviews and greater demands on clinical data quality and quantity (Majety *et al.*, 2021). Kearney and McDermott (2023a) reported that approximately 40% of medium-risk device manufacturers and approximately 45% of high-risk devices had experienced inconsistencies in the amount of clinical data accepted by NBs. They cited that further clarification from the European Commission regarding their expectations on what constitutes sufficient clinical evidence for specific types/groups of devices is required. They further stated:

> Confusion regarding how much clinical data is required is likely to continue resulting from inconsistent demands being placed on the notified bodies from each individual competent authority, and these, in turn, being passed down to the manufacturer.

A further potential challenge lies in that, historically, manufacturers may have relied on demonstrating equivalence to a marketed device in support of regulatory approval, thereby reducing the burden on them to generate their clinical data (Sorenson and Drummond, 2014). However, the MDR introduces stricter criteria for demonstrating equivalence. If the manufacturer cannot obtain sufficient data to demonstrate conformity to the new criterion, they cannot rely on equivalence and must generate their clinical data to support CE marking (Medical Device Coordination Group, 2020). Therefore, clinical investigations may represent the

only viable option for generating sufficient clinical data for certain high-risk and legacy devices that can no longer rely on demonstrating equivalence. However, the high costs associated with clinical investigations can make them restrictive, particularly if the cost of generating the required clinical data outweighs the potential return on investment (Melvin *et al.*, 2023).

The challenges faced by medical device manufacturers in meeting the strengthened clinical evaluation requirements pose a potential risk to the health-care ecosystem (Kearney and McDermott, 2023b). This is because manufacturers may have decided to discontinue certain medical devices, leading to their removal from the EU market (Malvehy *et al.*, 2022). According to Kearney and McDermott (2023a), in their survey of manufacturers, 54% of the study respondents reported that their company intends to remove devices currently CE-marked under the directives from the EU market. Possibly one of the most challenging requirements detailed in MDR Article 65. In some cases, the launch of innovative medical devices has been postponed, thereby preventing access to the patients that need them (Behan *et al.*, 2017; Malvehy *et al.*, 2022). The MDR represents a significant change in the regulation of medical devices in Europe. Without a complete library of supporting guidelines and documents from the European Commission, the transition from the directives to the MDR poses a steep learning curve for all stakeholders. Considering that the MDR came fully into force in May 2021, manufacturers were under pressure to obtain CE marking under the MDR or risk removal of their devices from the EU market. Clinical evaluation is a complex and multifaceted topic. Several authors report that compliance with the MDR's clinical evaluation requirements poses a significant challenge for manufacturers (Behan *et al.*, 2017; Holborow, 2021; Valla, 2021). However, to the authors' knowledge, other than mixed-methods studies, for example, by Kearney and McDermott (2023a, 2023b), there is no published literature study or other data identifying the specific elements of the clinical evaluation that pose the greatest barriers to ensuring MDR compliance, hence the novelty of this study. Thus, the value of this research is that it will provide a unique insight into the specific challenges faced by manufacturers in addressing the strengthened clinical evaluation requirements and the strategies adopted by manufacturers to comply with the new requirements. By establishing the challenges therein and understanding them, recommendations can be put forward to aid manufacturers, and thus this study will have implications for theory and practice.

Based on the research outcome, the researcher aims to identify opportunities to develop targeted resource material to support manufacturers.

Within this context, this research project will investigate the advantages, challenges and critical success factors (CSFs) faced by medical device manufacturers when generating their clinical evaluation under EU-MDR 2017/745:

- What literature is available related to CER changes in the new MDR?
- What advantages are there to the new CER changes in the MDR?
- What challenges are faced by manufacturers when generating an MDR-compliant CER?
- What are the CSFs for completing device CERs?

Section 2 will provide the background literature related to the MDR and CER requirements. Then, Section 3 outlines the methodology, and Section 4 outlines the results. Finally, the discussion and conclusion are outlined in Sections 5 and 6.

2. Background to this study

2.1 Introduction to European Union medical device market

Europe represents the second largest market (approximately 27%) for medical devices and is predicted to increase in value from US$140.07bn in 2022 to US$171.9bn by 2027. While the

USA represents the largest market for medical devices, manufacturers have historically viewed Europe as a more attractive market, and indeed many have taken the strategic decision to launch their product on the EU market first, followed by the US market at a much later stage. This decision has been attributed to various factors, including lower demands for pre-market clinical data, compared to the USA, often limited to providing evidence from literature reviews for similar devices, laboratory testing or small-scale clinical investigations (Vasiljeva *et al.*, 2020; Hwang *et al.*, 2016). The lower demand for clinical data resulted in some high-risk medical devices receiving approval for use in Europe, approximately Three to four years earlier compared to approval via the equivalent food & drug administration (FDA) premarket approval (PMA) pathway (Hwang *et al.*, 2016; Migliore, 2017; Makower *et al.*, 2010). The FDA also describes 12 high-risk medical devices approved for use in Europe based on limited testing but were later found to be unsafe and ineffective and ultimately withdrawn from the European market.

2.2 European Union CE marking process

To place a medical device on the European market, it must be CE-marked. The purpose of the CE mark is to demonstrate to all relevant stakeholders that the medical device is safe for use, performs as intended and that the manufacturer and medical device conform to the applicable regulatory requirements (European Commission, 2022).

The device's technical documentation, including the CER, is used by the manufacturer to demonstrate device safety and performance and is, therefore, a key component of the CE marking process. The NB assesses the technical documentation, and a CE mark is issued if the evidence supports the conclusion that the device is safe and performs as intended in accordance with the manufacturer's intended use statement. In addition, once marketed, the ongoing safety and performance of the device are monitored throughout its lifetime using the manufacturer's PMS system. As part of their surveillance activities, the competent authority in each member state and the approving NB are also responsible for monitoring the safety and performance of the marketed devices.

2.3 Introduction to European Union-MDR 2017/745

Since the early 1990s, medical devices in Europe were governed under two directives, namely, Council Directive 93/42/EEC on Medical Devices (MDD) (1993) and Council Directive 90/385/EEC on Active Implantable Medical Devices (AIMDD) (1990). However, in response to:

- the well-publicised poly implant prothese breast implant scandal and the metal-on-metal hip implant incident (Cohen, 2012);
- concerns regarding the lack of transparency and inconsistency around how medical devices are approved by different NBs (Melvin and Torre, 2019; Cohen, 2012; Cohen and Billingsley, 2011; Sorenson and Drummond, 2014); and
- recognition that the directives were not appropriate for regulating the rapid advances in technology including the explosion in digital health devices, the European Commission took action to strengthen the medical device regulatory framework (Sorenson and Drummond, 2014).

As a result, a comprehensive review process culminated in the publication of a new MDR, which replaces both the MDD and AIMDD.

Because of the COVID-19 pandemic, The MDR entry into force was extended by 12 months, and the MDR came fully into force on 26 May 2021. From this date, new medical devices can

only be placed on the market if they are CE marked under MDR. Post May 2024, legacy devices already legally on the market can continue to be put into service until May 2025.

As MDR is a regulation, it applies to each EU member state without modification (Vasiljeva *et al.*, 2020). The change from directive to regulation is intended to allow for greater consistency in MDR across all member states, thereby providing greater assurance and confidence to all stakeholders involved in the medical device supply chain, including regulatory bodies in other jurisdictions, regarding the high standard of MDR across Europe.

2.4 Structure and key changes

MDR is a 175-page document, making it significantly longer and more complex than its predecessors (MDD 93/42/EEC – 60 pages and AIMD 90/385/EEC – 20 pages). Chapter VI Article 61 on clinical evaluation references the requirement to conform to the general safety and performance requirements, which are described in Annex I. Chapter VI Article 62 requires a clinical investigation to be conducted as described in Annex XV. The correlation between the MDR, the MDD and AIMDD is also detailed in Annex XVII, providing a useful guide to facilitate the transition from the directives to the Regulation. The MDR introduces new requirements and enhances key regulatory elements of its predecessors. However, the biggest overhaul to the regulation relates to strengthening the clinical evaluation requirements. For example, for high-risk class III and implantable devices, evidence of device safety and performance must be generated through clinical investigations and for all devices, the CER must be updated using PMS data and aligned to the risk management system. Several authors report that demonstrating compliance with these requirements represents one of the biggest challenges for medical device manufacturers (Behan *et al.*, 2017; Holborow, 2021; Valla, 2021).

The MDR also introduces a clinical evaluation consultation procedure and scrutiny procedures. These new procedures are designed to enhance oversight of the NBs by the relevant competent authority by sampling their assessment of the manufacturer's CER. In addition, for certain high-risk devices, the NBs' clinical evaluation assessment reports must be scrutinised by expert panels. Given this additional level of scrutiny, manufacturers can, in turn, expect their clinical evaluations to be a key focus area during the initial CE marking process and subsequent PMS activities.

3. Methodology

The primary methodology used in this research was a systematic literature review (SLR). The SLR process, developed for medical research, follows the rules and guidelines to help researchers perform a structured, repeatable and independent review that identifies, assesses and synthesises literature to answer a research question (Kitchenham, 2004; Tranfield *et al.*, 2003). The systematic nature of the literature review enables a detailed review screening and analysis of the available literature (Dezi *et al.*, 2018; Madanaguli *et al.*, 2022). The method used was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines (Page *et al.*, 2021). The methodology followed the following four stages:

(1) planning;
(2) screening;
(3) analysis; and
(4) reporting and discussion stage.

3.1 Planning stage

First, we constructed two search strings to find the relevant papers to answer *RQs* 1, 2, 3 and 4 (Figure 1). Then, a review protocol was planned and carried out by identifying, selecting and analysing the relevant thematic papers and subsequently, results were disseminated (Pandey *et al.*, 2020). The semi-systematic review approach was chosen as its design suits topics that have been conceptualised differently and studied by various groups of researchers within diverse disciplines, and that hinders a full systematic review process (Wong *et al.*, 2013). Furthermore, the semi-SLR process lends to more development and tailoring to specific project research areas. In this research, the authors analyse specifically legislative and government regulatory documents and enacted laws related to European

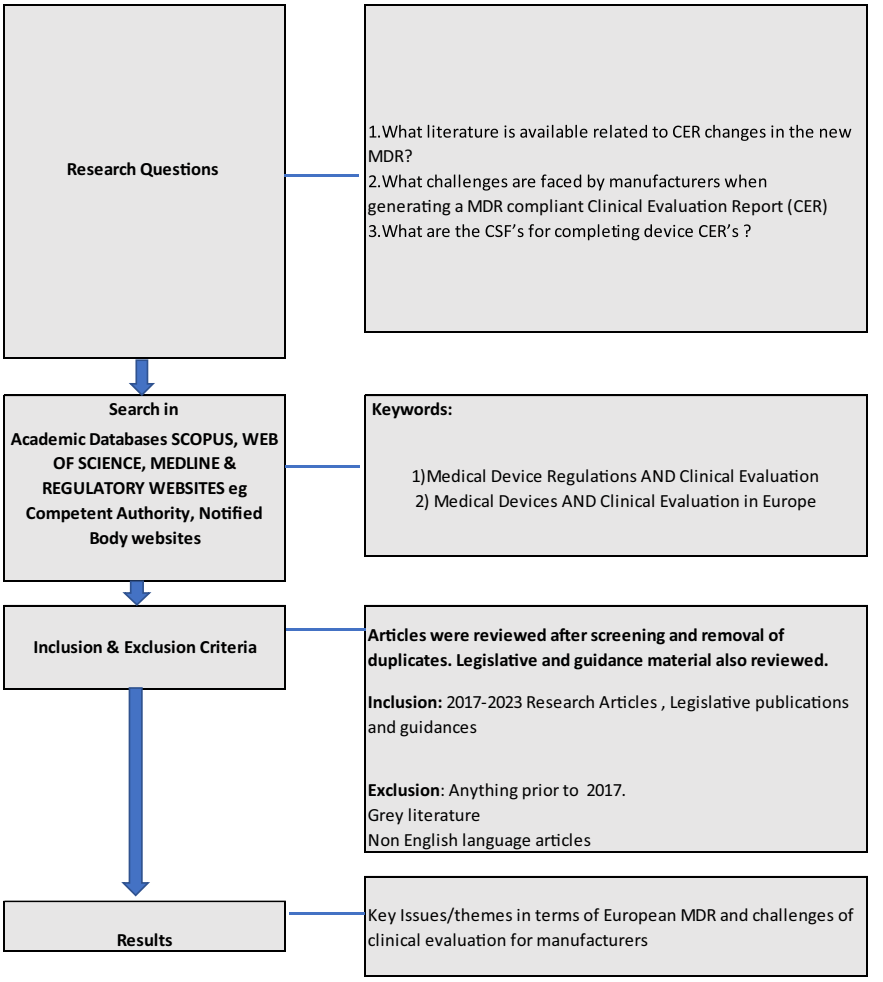

Figure 1.
SLR flow chart

Source: Authors' own work

medical devices and the European MDR and journal articles on European medical devices legislation, particularly from a clinical viewpoint.

3.2 Screening stage

The authors searched articles in academic literature databases Google Scholar, Scopus, MEDLINE and Web of Science using search strings such as "Medical Device Regulations AND Clinical Evaluation" and "Medical Devices AND Clinical Evaluation in Europe" the authors carried out an iterative search for each string.

As the MDR legislation has only come into force in Europe since May 2021, it was irrelevant to review the literature before 2017, when the regulations were first announced. Also, as manufacturers are adapting to the new legislation and engaging in compliance, the new regulations' challenges in clinical evaluation requests are only being reflected in the literature in recent years.

In addition to the academic database search, Google search engines and author knowledge were used to access and identify competent authority websites and NB websites to review white papers and expert updates. For example, the websites of the European Medicines Agency (EMA), Health Products Regulatory Association (Ireland) (HPRA) and British Standards Institute (BSI), to name but a few, were reviewed.

3.3 Analysis stage

The final screened documents were then analysed. Articles or guidance related to the legislation in terms of clinical evidence found as a result of the search were then reviewed. Abstracts of articles were scanned for their relevance, selected if appropriate, and read and cited if relevant to the research questions. Duplicate academic papers, for example, were removed. Following the selection of 28 relevant peer-reviewed papers (as well as the selection of relevant regulations and guidance), more in-depth reading and thematic analysis were carried out.

3.4 Reporting and discussion stage

The results of the SLR were summarised and discussed via thematic analysis related to the *RQ's* and challenges posed by increased CE in MDR, the critical success factors for successful CE under MDR, the advantages of increased CE under MDR and recommendations for successful CE under MDR. These discussions are discussed further in Sections 4 and 5.

4. MDR and clinical evaluation requirements

4.1 Overview of European Union Medical Device Regulations 2017/745 clinical evaluation

Clinical evaluation is defined by the MDR as "a systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer". The clinical evaluation process can be described in six steps, from establishing a clinical evaluation plan (CEP) to preparing the CER. The word "continuously" in the definition means that the clinical evaluation is not just completed once as part of initial CE marking but must be kept up to date throughout the lifetime of the medical device (Holborow, 2021). The definition also clarifies that the purpose of the clinical evaluation is to provide evidence that the device is safe for use and performs as intended and to confirm that the device is providing a clinical benefit to the patient or, in other words, that the device leads to an improvement in their quality of life, which would otherwise not have been possible with an alternative treatment option. Finally, the evidence that supports the

clinical evaluation must be derived from clinical data relevant to the medical device and/or an equivalent marketed device.

Clinical data is derived from multiple sources, including clinical investigations, peer-reviewed literature reviews, PMS activities, including post-market clinical follow-up (PMCF) and vigilance activities (e.g. complaints, adverse events, serious incidents and undesirable side effects). In addition, data from the risk management process, particularly conclusions regarding the acceptability of the benefit-risk ratio, also feed into the clinical evaluation (Holborow, 2021; Valla, 2021).

The strategy for identifying, appraising and analysing the clinical data must be carefully planned and documented in the CEP, detailed in MDR Annex XIV Part A. Furthermore, to draw valid conclusions, the clinical data's quality and scientific validity must be carefully assessed to determine its suitability. Therefore, the clinical evaluation must be completed by individuals or a multidisciplinary team with demonstratable competency (European Commission, 2016).

The results and conclusion of the clinical evaluation and the supporting clinical evidence are documented in the CER, and the NB subsequently assesses it. This assessment aims to ensure that the manufacturer has provided sufficient evidence to demonstrate device safety and performance and to support their conclusions regarding the benefit: risk profile. As previously mentioned, the NB's assessment of the manufacturer's CER is subject to scrutiny by the relevant competent authority, and in turn, manufacturers can expect their CER to be rigorously assessed by the NB. For certain high-risk devices (Class III implantable and Class IIb devices intended to administer and/or remove medicine) the NBs' assessment of the clinical evaluation is also subject to additional scrutiny by an expert panel. Post CE marking, the CER must be kept up to date using data collected through the PMS system and is subject to further review as part of its NB's surveillance activities.

To ensure that the CER can stand up to this level of scrutiny, manufacturers must implement a clinical evaluation strategy that is designed to obtain reliable, high-quality and scientifically valid clinical data not only as part of the initial CE marking but throughout the lifetime of the medical device (Holborow, 2021; Valla, 2021; Holborow, 2022); otherwise, there is a risk of delays in the initial CE marking process or the removal of the device from the market (Behan *et al.*, 2017; Malvehy *et al.*, 2022).

4.2 Clinical evaluation – pre-market clinical data sources

For initial CE marking, the primary clinical data sources are peer-reviewed scientific faced scientific literature reviews refer to articles written by experts in their field about a particular medical device or medical intervention. For example, Sorenson and Drummond (2014) conducted a systematic review to investigate the revision rates of metal-on-metal hip implants. However, a challenge with this methodology is that peer-reviewed literature may not be available for the device itself, including the different variants, sizes and accessories, or for the specific clinical conditions the device intends to address (Holborow, 2021). Furthermore, there may be gaps in the published information, hindering manufacturers' ability to draw scientifically valid conclusions (Medical Device Coordination Group, 2020).

Furthermore, the published article(s) may not sufficiently detail the technical, biological or clinical characteristics to enable the manufacturer to demonstrate equivalency under the MDR. The outcome of the literature review, including the protocol used, search engine, inclusion/exclusion criteria, article appraisal strategy, results and conclusions, must be documented (European Commission, 2016). Any identified data gaps require supplementation with clinical data obtained from other sources.

Clinical investigation refers to the formalised assessment of the safety and performance of a medical device in one or more human subjects. The results of high-quality clinical investigations (i.e. those conducted per ISO 14155 clinical investigation of medical devices for human subjects – good clinical practice) represent the highest-ranked source of clinical data (MDCG, 2020). In simple terms, a clinical investigation seeks to answer the following questions in a sample of the target population: "Does the medical device operate as expected? Does the medical device deliver the required health benefit to the patient? Are the safety controls that were designed for the medical device effective? and Are there any previously unidentified side effects or safety risks associated with the use of the medical device?" (Ivanov *et al.*, 2019).

Under the directives, demonstration of device equivalency was commonly used to circumvent the need to conduct clinical investigations. Using this approach, manufacturers could claim that their device has a similar level of performance as a currently CE-marked device or devices. However, under the MDR, demonstration of equivalence for implantable and class III medical devices requires the manufacturer to implement a contract with the second manufacturer granting them full access to the equivalent device's technical documentation on an ongoing basis, and the equivalent device's clinical evaluation must be sufficient to demonstrate conformity with the MDR. As the second manufacturer may be a competitor, securing this contractual agreement will likely prove challenging. In addition, for implantable and class III medical devices, a clinical investigation may be required for initial CE marking (Holborow, 2022).

In the case of Class IIa and IIb devices, equivalence to a CE-marked device or devices can be used without the need for a contract or agreement with the manufacturer of the marketed device. However, the CER must contain sufficient clinical data to demonstrate that the device's technical, biological and chemical characteristics are similar to those of the marketed device and that there are no clinically significant differences in safety or performance (Medical Device Coordination Group, 2020). Accessing sufficient clinical data to demonstrate this level of equivalence may prove challenging, particularly in the absence of access to the marketed devices' technical documentation and the lack or absence of appropriate peer-reviewed published literature (Holborow, 2022). If the manufacturer cannot demonstrate equivalence, gaps in clinical data will need to be addressed via other means, including clinical investigations (Medical Device Coordination Group, 2020; Holborow, 2022).

Randomised control trials (RCTs) are a type of clinical investigation whereby one study population is treated with a medical intervention and compared against a second control population who receives either no intervention or an alternative intervention, and they represent the gold standard for generating clinical data. However, RCTs are exposed to several limitations, including but not limited to ethical considerations particularly for novel devices designed to treat a particular condition for which there is no suitable alternative (Tarricone *et al.*, 2016), end user experience/learning curve which may negatively impact on the reported effectiveness of the treatment (Tarricone *et al.*, 2016; Pongiglione *et al.*, 2021; Pelayo *et al.*, 2021), challenges with randomisation and blinding (Tarricone *et al.*, 2016; Pongiglione *et al.*, 2021; Pelayo *et al.*, 2021), timing of the clinical investigation in relation to finalisation of the design particularly as the design if often tweaked and modified based on initial user feedback (Pelayo *et al.*, 2021), lack of expertise in relation to trial design particularly for small and medium enterprise (SME) companies, failure to determine appropriate clinical outcomes, study participants may not reflect real-world populations (Klonoff, 2020), small sample size (Melvin and Torre, 2019; Pelayo *et al.*, 2021), duration of the clinical trial compared to expected lifetime of the medical device (Melvin and Torre, 2019) and restrictive costs which is a key limitation for smaller companies.

In response to these challenges, many experts in the medical device sector are looking at alternative or supplementary approaches to traditional clinical investigations, including harnessing the power of data and information generated from real-world use of the medical device (Klonoff, 2020; Pongiglione *et al.*, 2021; McDermott and Kearney, 2023).

4.3 Clinical evaluation – post-market clinical data sources

Once a medical device is on the market, the manufacturer must continue to collect and analyse data for the early identification of safety alerts and for updating the clinical evaluation. The primary sources of post-market clinical data include published scientific literature reviews and PMS, including PMCF. Compared to the directives, MDR introduces detailed and more prescriptive requirements for PMS and PMCF. To address these requirements, manufacturers will be tasked with updating and, perhaps, rethinking their current processes to ensure compliance with MDR. Furthermore, for legacy devices, the requirements for PMS and PMCF are effective immediately from May 2021, and NBs will verify compliance as part of MDD/AIMDD surveillance activities (Medical Device Coordination Group, 2021).

4.4 Post-market surveillance system

The PMS system is an important element of the manufacturer's quality management system (QMS) and is designed to collect safety data, information and experience from real-world use of the marketed device for the duration of its lifetime. The outputs of the PMS system are also used to update the risk management file and clinical evaluation. PMS activities can be reactive or proactive. Reactive PMS activities can include analysing customer complaints, serious incidents, field safety corrective actions, maintenance/service reports, performing literature reviews, reviewing periodic safety update reports (PSURs) and data trending. Proactive PMS is when the manufacturer actively seeks data and information on their device using measures such as gathering feedback from focus groups, conducting patient/end-user surveys, monitoring recalls or other safety issues associated with similar medical device and obtaining information from device registers and/or databases (Melvin and Torre, 2019).

4.5 Post-market clinical follow-up

PMCF refers to the proactive collection and evaluation of clinical data from the actual use of the medical device throughout its lifetime. It is a subset of the PMS system and is used to bridge any gaps in knowledge regarding safety and performance and/or address new safety concerns and emerging risks identified as part of the PMS activities or market surveillance activities. Clinical data generated through PMCF is also used to:

- support the device benefit-risk ratio;
- support the claimed lifetime (Holborow, 2021); and
- verify that the intended purpose statement is correct (Medical Devices Coordination Group, 2020).

PMCF is required for all devices unless a valid justification can be provided. PMCF data generated under the directives may not be sufficient to demonstrate compliance with the EU-MDR, particularly for devices that can no longer claim equivalence. Therefore, manufacturers of legacy devices need to consider the role of PMCF activities as part of their EU-MDR transition strategy in accordance with MDCG 2020-6 (MDCG, 2020).

PMCF activities are typically categorised as a study or survey designed to answer specific safety and performance questions and are conducted using a planned and

systematic approach. Surveys include questionnaires and interviews and are typically administered to the device user to gather data on usability, user experience, patient outcomes, opportunities to improve the device, etc. Surveys are less time-consuming and less expensive than PMCF studies, however as surveys can be subjective, the scientific validity of the resulting clinical evidence is typically regarded to be of lower quality compared with evidence derived from other sources (MDCG, 2020). Therefore, the adoption of surveys must consider the risk class of the device and the quantity and quality of previously gathered data. A PMCF may include new clinical investigation, PMCF clinical investigation, pre-market follow-up and real-world evidence (RWE). Interest is growing in the conduct of PMCF studies, which harness the power of RWE. Interest in RWE is being driven by the recognition that a wealth of valuable data is generated from real-world use of the device, including information on off-label use, and this data may be useful for providing a more accurate reflection of long-term device safety and performance. Interest in the use of RWE is further driven by the explosion in digital medical devices, which have the potential to provide a wealth of real-time clinical data over the lifetime of the medical device.

4.6 Relationship between clinical evaluation and post-market surveillance system

The manufacturer's clinical evaluation and PMS systems are interrelated. Post CE marking, data on the device's use is collected per the manufacturer's PMS and PMCF plan. As appropriate, the collected data is analysed and documented in the manufacturer's PMCF, vigilance and trend reports. For class I devices, the PMS report is updated as needed based on the outcome of the PMS activities. For Class IIa, IIb and III devices, the results and conclusion of the analysed PMS data will be used to update the PSUR – annually for class IIb and III, and every two years for IIa in accordance with MDR article 86. In addition, throughout the medical device's lifecycle, in accordance with MDR articles 61(11) and 83(3), the manufacturer must update the clinical evaluation and risk management file using this data and based on the outcome, initiate a new PMCF if required. As part of the transition to the MDR, manufacturers need to consider how these processes will work together to provide a proactive approach to ensuring safety and performance for the device's lifetime.

5. Discussion of the literature review findings

Having presented the background to the study and the summary of the literature related to the new MDR regulations requirements for increased clinical evaluation, the results of the *RQs* are discussed below. The themes of the advantages of the new MDR clinical evaluation requirements, the challenges of the clinical evaluation process and the CSFs of conducting the clinical evaluation as per the *RQs* are summarised.

5.1 Review of the literature (RQ1)

The literature on clinical evaluation under the new MDR was sparse and limited. Although many academic papers related to medical devices generally referenced the new MDR, they lacked specific details related to the new CER requirements. Therefore, while many articles were referenced in this study to provide context and background to the new MDR and clinical evaluation requirements, only 28 articles from academic databases were selected as a result of a potential initial 2,276 articles that were found using the initial search strings. Figure 2 demonstrates that the number of publications related to clinical evaluation and the new MDR has been minimal (as per our selection and screening) since the announcement of the MDR in 2017. Some of the papers selected particularly from 2020 onwards were included in the selection for review as they provided some background related to the EU-MDR and CE but did not discuss in great detail the challenges therein. Now that the MDR is in force, it

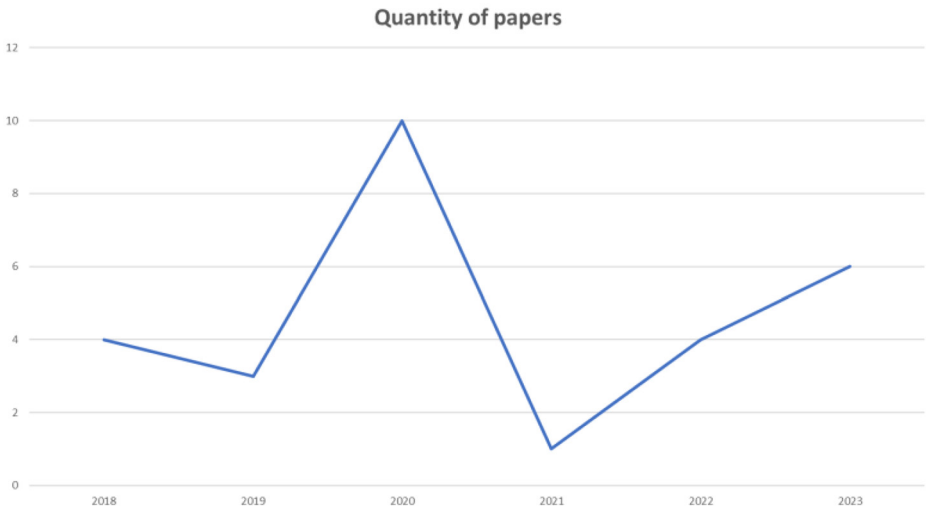

Figure 2.
The number of publications with a MDR clinical evaluation-specific theme since 2018

Source: Authors' own work

would be expected to see an increase in the literature related to clinical evaluation and practical case studies once manufacturers and device developers gain more understanding and practical knowledge of the regulations.

5.2 Advantages of the new regulations and the increased clinical evaluation requirements (RQ2)

Although there were mixed viewpoints in the literature on the advent of the new MDR regulations and specifically related to the increased clinical evaluation aspects, overall, the changes were perceived for the greater good. Overall, the MDR requirements should not just be seen as an obstacle in the medical domain but as a chance to provide new opportunities for innovation (Bianchini and Mayer, 2022). The MDR's approach to device safety and performance and its implications for device design and development are game-changers in the medical device industry (Ben-Menahem *et al.*, 2020). The MDR introduces more devices subjected to a higher degree of scrutiny before entering the market with more stringent requirements on clinical evaluation, including the requirement for appraisal of clinical data and new requirements for PMS, which may help spot early on any new, unexpected side effects and risks of the devices (Niemiec, 2022). The new clinical evaluation requirements will necessitate a closer collaboration between industry and registries to evaluate the safety and performance of high-risk devices (Burri and Spoerri, 2020). Customers of medical device manufacturers will now have a legitimate claim that a medical product is safe and effective, regardless of how new the technology is or the manufacturer's economic situation with the new MDR (Berensmann and Gratzfeld, 2018).

The new legislation states that:

> Transparency and adequate access to information, appropriately presented for the intended user, are essential in the public interest, to protect public health, to empower patients and healthcare professionals and to enable them to make informed decisions, to provide a sound basis for regulatory decision-making and to build confidence in the regulatory system. (MDR)

In the past, it was difficult to gain access to the information that led an NB to issue a certificate of conformity for a device. However, this transparency concept will increase under the MDR, as the manufacturer must publish a summary of safety and clinical performance (SSCP) for high-risk devices and keep this updated on an annual basis, which will be available on the EUDAMED database, which will be accessible publicly and is a critical element of the new system (Byrne, 2024). Fraser *et al.* (2021) further stated that this increased clinical evidence and SSCP being publicly available in the Eudamed will facilitate evidence-based choices of which devices cardiologists and health-care professionals to recommend and use.

Niemiec (2022), in a study on the effect of the new regulation on artificial medical intelligence (AI) devices, found that MDR will likely help improve the safety and performance of medical AI devices on the European market. Furthermore, the requirements for clinical evaluation in the regulation, in particular the requirement for the appraisal of clinical data, may increase the attention paid by manufacturers and NBs to the quality of clinical evaluation and contribute to its improvement.

Before the revision of MEDDEV 2.7/1 in 2016, CERs were produced when required and summarised based on the clinical evidence available up to that point in time. Therefore, the introduction of the CEP was a significant change in the clinical evaluation process and was a progressive precursor to the MDR. The MDR has expanded risk assessment, focusing more on the benefits of a medical device and more on PMCF (Pritchard, 2022). The entire clinical evaluation process is now much more planned, objective, robust and comprehensive than it used to be.

Finally, the impact of the new MDR and the economic crisis associated with COVID-19, while being fatal for many manufacturers, represents a unique opportunity for mergers and acquisitions for others (Pelayo *et al.*, 2021).

5.3 Challenges for clinical evaluation for manufacturers under Medical Device Regulations (RQ3)

While the literature was positive on the advent of the new MDR clinical evaluation requirements, the vast majority of the literature was concerned about the challenges of providing this information (Pritchard, 2022; Bianchini and Mayer, 2022; Ben-Menahem *et al.*, 2020; Kearney and McDermott, 2023a, 2023b).

Egbosimba (2019), in his paper "Medical devices industry: the problem of clinical evaluation reports", stated that the scope of the new MDR requires many manufacturers to assess their documentation in relation to their entire product portfolio. To write a compliant CER, this should be based on a comprehensive clinical evaluation strategy, but this is often beyond the competencies of non-CER staff. Lack of experience, resources and time in producing sufficiently supported CERs is, therefore, a huge challenge with varying interpretations of the available clinical evaluation guides. As a result, many manufacturers write CERs on an *ad hoc* basis instead of regularly updating a product's entire life cycle. Suppose the scientific literature used during a clinical evaluation is not conclusive enough or not fully applicable to the product under focus. In that case, clinical trials must be conducted and evaluated, and also, an initial evaluation must be carried out during development, with the clinical evaluation required to be updated regularly. Berensmann and Gratzfeld (2018) found that for manufacturers of device apps and wearables, this sometimes results in considerable costs. It is also a major challenge for small manufacturers and device start-ups that could stifle innovation. Baines *et al.* (2022) cited the MDR as "killing innovation". Ben-Menahem *et al.* (2020) echoed the concerns in relation to smaller manufacturers caused

by the increasing complexity of the regulatory process on medical-device innovation in start-ups and smaller companies.

According to Stern (2017), these start-ups' market entry depends on their ability to overcome regulatory uncertainty, and their lack of expertise in quality management, regulatory affairs and clinical evaluation makes interpreting and translating the MDR into formal processes difficult. Whereas larger companies with broad product portfolios can more easily absorb the new MDR requirements, increased regulatory compliance costs and the longer time-to-market for new devices will require start-ups with little or no revenue and single-technology companies to seek partnerships with larger manufacturers to build their capability and capacity to deal with the new MDR (Ben-Menahem *et al.*, 2020; Pelayo *et al.*, 2021). The European Commission acknowledges the increasing costs for SMEs yet anticipates that the MDR will benefit these smaller players' competitive position by increasing the public's confidence in the system and offering companies a uniform and clear procedure across all EU member states(Ben-Menahem *et al.*, 2020). However, Melvin (2022) has outlined that the MDR does not have special provisions for therapeutic orphan devices, characterised by low-volume sales and a reduced return on investment. In addition, some concerns increase compliance requirements, and any change in the time or cost to market leaves these products particularly vulnerable to withdrawal (Kearney and McDermott, 2023a, 2023b; Carl and Hochmann, 2023; Guerlich *et al.*, 2023).

Much time has to be factored into clinical evidence gathering, and time is unaccounted for in most calculations when considering clinical evaluation, an activity often requiring significant investor support (Baines *et al.*, 2022). The lack of understanding and confusion regarding sufficient clinical evidence and enough clinical evidence was reflected in a qualitative study of medical device stakeholders in 2022 by Baines *et al.* (2022) and in two studies, a quantitative and qualitative study by Kearney and McDermott (2023a, 2023b). A further survey study by Carl and Hochmann (2023) surveying the German orthopaedic industry before and after the MDR implementation found similar challenges to those mentioned above. Additional workload for technical documentation, increased resource expenditure and cost and a lack of clarity in relation to the new requirements of the MDR were among the top challenges for companies, according to that study.

Ben-Menahem *et al.* (2020) highlighted that few members of the EU's clinical community have the combination of expertise in the new regulatory process for medical devices, the correct clinical use of device technologies and device-risk management. Another concern related to the stricter MDR and stricter clinical evidence requirements CE requirements was the amount of NBs that have closed down or declined to apply to be designated to the MDR for certifying certain device types due to the increased stringency and scrutiny and specialist knowledge imposed on their operation (Garzotto *et al.*, 2022; Pelayo *et al.*, 2021). The medical devices coordination group (MDCG) and the competent authority for medical device group issued communications regarding the challenges of NB capacity (Melvin, 2022). As of December 2022, there were only 36 NBs designated to process around 23,000 certificates by May 2024 if all current devices were to stay on the market (Taylor, 2022). Melvin *et al.* (2023), in their paper on discussing the availability of orphan and paediatric devices, advised that paediatric cardiologists in Europe needed to be aware that certain medical devices may become unavailable over the next two years. Unfortunately, these concerns about shortages of device supplies have been realised. For example, Guerlich *et al.* (2023) highlighted that several high-risk paediatric medical devices have become unavailable in the EU due to the EU-MDR. As a result, the EU-funded CORE-MD project has developed recommendations evaluating and certifying high-risk medical devices for paediatric device market introduction (Melvin *et al.*, 2023).

Fraser *et al.* (2021) were more critical in stating that while the MDR provides general principles for clinical investigations, it provides few methodological details, which challenges competent authorities to set appropriate balances between regulation and innovation, pre- and post-market studies, clinical trials and real-world evidence.

Manufacturers have historically viewed Europe as a more attractive market, and indeed, many have taken the strategic decision to launch their product on the EU market first, followed by the US market at a much later stage. This decision has been attributed to various factors, including lower demands for pre-market clinical data compared to the USA, often limited to providing evidence from literature reviews for similar devices, laboratory testing or small-scale clinical investigations (Vasiljeva *et al.*, 2020; Hwang *et al.*, 2016). The lower demand for clinical data resulted in some high-risk medical devices receiving approval for use in Europe, approximately three to four years earlier compared to approval via the equivalent FDA PMA pathway (Hwang *et al.*, 2016; Migliore, 2017; Makower *et al.*, 2010). In addition, in contrast to the USA, manufacturers were historically not required to provide evidence that the device benefits the patient (Sorenson and Drummond, 2014). However, this trend to launch in Europe first is reversing due to the new MDR. In a year after the EU-MDR went into effect, a report published by the Boston Consulting Group and UCLA Biodesign shows that the new regulation has slowed the pace of medical device innovation in the EU (Johnson *et al.*, 2022). Kearney and McDermott (2023a, 2023b) also found in their studies that many organisations were considering removing devices from the market due to increased clinical regulations, with many outsourcing their CER's due to resource issues.

5.4 Critical success factors for clinical evaluation in the new MDR (RQ4)

Because of the importance of the CER being approved by an NB to keep that device concerned on the market and maintain revenues and manufacturer reputation, a clear and proactive strategy for CE is necessary (Egbosimba, 2019). Ben-Menahem *et al.* (2020) discussed the importance of manufacturers following a more stringent risk-management process that is strongly linked to clinical evaluation with continuous clinical input and evaluation by clinical experts in the early stages of product conceptualisation and development with assessment in a therapeutic area and in the various environments where practitioners use the device. Bringing in clinicians in the early development stages is also essential for ensuring that the product meets the safety and performance requirements in the clinical setting.

In terms of CER design, medical writers should be aware of existing implant registries, understand what characteristics make a registry suitable to support regulatory requirements and recognise both the value and the limitations of registries as a source of clinical evidence (Burri and Spoerri, 2020). In addition, writers should be familiar with the IMDRF registry requirements to assess the suitability of registry data for regulatory submissions.

A high-quality CER could take up to three months or longer depending on available resources and expertise, and thus, training programs for different aspects of the CER process are important to develop the necessary tools to facilitate the process over time. Using internal or external resources, each manufacturer should create a standardised approach for CER report writing to avoid discrepancies and errors, facilitating the work of the NB, and encourage the participation of different actors and multiskilled team involvement within the company to save time and improve the report quality (Egbosimba, 2019). The balance between day-to-day work tasks and writing CERs will be important, and many organisations are outsourcing the writing of the CERs (Kearney and McDermott, 2023b).

In summary, irrespective of device risk classification according to Kearney and McDermott (2023b) in their study of the MDR challenges "determining the level of clinical evidence required to demonstrate compliance with the MDR poses the greatest challenge for medical device manufacturers". They further stated that this issue is exacerbated by "the lack of consistency regarding the level of evidence that different notified bodies are willing to accept".

They further found that the device manufacturers were using several different data sources to generate their CERs including referring to Medical Device Co-ordination group guidance documents, internal knowledge transfer, NB publications and/or external training to upskill their employees in this area. However, they found that there existed:

> A knowledge gap in terms of understanding the interface between regulatory affairs and QMS process interaction, understanding the strength and limitations of different clinical data sources, and conducting a regulatory-acceptable literature review.

The changing regulatory framework will require larger device manufacturers to re-evaluate their product portfolio and marketing strategy. Depending on how markets develop, a "rationalisation" of product portfolios is important to establish what clinical evidence is needed (Ben-Menahem *et al.*, 2020). However, this rationalisation may also lead to supply chain shortages of devices.

However, a CSF of the impact of the regulation depends on its adequate enforcement by the EU member states (Niemiec, 2022). Adhering to MEDDEV 2.7/1 (rev. 4) and following the guidance on the evaluation of the methodological quality of studies will aid in ensuring enforcement by outlining specific issues that should be critically appraised, such as the appropriateness of sample size, the power of calculations, the endpoints and controls used and the validity of conclusions. Furthermore, according to Pelayo *et al.* (2021) and McDermott and Kearney (2023), regulatory bodies should broaden their perspectives and request more real-world performance monitoring rather than post-marketing surveillance alone to maximise the safety and efficacy of MDs.

5.5 Where are we now?

In response to supply chain concerns, the EU Health Commissioner Stella Kyriakides in December 2022 sought to seek to pair the delay with "additional measures to address the structural problems" of MDR, including the need for targeted solutions to the problems facing rare disease devices. Fick (2022) reported that the EU saw challenges in implementing the MDR, threatening supplies of critical devices, such as catheters used for surgeries on newborns with heart conditions. The implemented amendment to the MDR legislation Regulation (EU) 2023/607 was passed into law early in 2023 and will give the EU, manufacturers and NBs four to five years, depending on the risk classification of a device, to fix the problems that have forced officials to delay MDR twice already (Taylor, 2022). Thus, this regulation not only extended the transitional provisions of the MDR until 2028 for class I up classified devices but also removed the "sell-off provision" for both the MDR and in vitro diagnostic regulation. According to HPRA (2024):

> This means that devices already placed on the market can continue to be made available or put into service until the revised expiry of the certificate or until the shelf life of the device.

However, a potential knowledge gap exists when it comes to understanding the interface between regulatory affairs and QMS process interaction, understanding the strength and limitations of different clinical data sources, and conducting a regulatory-acceptable literature review. Identifying these gaps provides NBs and the Medical Device Co-ordination

group (with opportunities to develop guidance in these areas and educational training providers to target their course offerings to address these gaps).

6. Conclusion

There is a dearth of literature related specifically to the MDR requirements for increased clinical evaluation. While many papers referred to the clinical evaluation requirements, there was no in-depth analysis.

The new MDR and the requirement for increased clinical evaluation will ensure a safer device for customers and patients. However, manufacturers will face challenges in completing clinical evaluations and gathering data for their CER reports. Coupled with a backlog in NB's capacity to certify to the new MDR, there are documented supply chain shortages related to European devices, which may increase further. Manufacturers have adopted a "Europe last" approach and have started to carry out their clinical trials in the USA first, which is seen as a more manufacturing- and innovation-centred regulatory environment. The decision of the EU Health Commissioner to introduce an amendment to allow manufacturers and NBs to have more time to certify devices alleviated some concerns about device supply shortages but does not invalidate the aforementioned concerns or future shortages.

The study recommends that there is an opportunity for more training and clarification by the EU, NBs and MDCG to develop more clarity and education to address knowledge gaps in relation to conducting scientific reviews, writing CER's and how CE ties in with other risk-based systems and the QMS. There are also increased opportunities to use RWE and real world data in the CE process to help gain the CE mark for devices. There are opportunities for more policy amendments related to low-running, paediatric and orphan devices to prevent loss of supply and effects on patent safety. Regulatory sandboxes and pre-submission meetings may be an opportunity to ease the challenges faced by manufacturers in getting a CE-compliant device under the MDR.

Theoretical implications of this study include its enhancement of the current literature specifically related to understanding the impact of increased CE requirements under the MDR. This is the first SLR study specific to this area, bringing together all the published literature on the topic to date. The managerial implications are that this study substantially aids manufacturers, NBs and indeed regulators alike in combining the challenges for CE under ME and explaining both the requirement and implications. From a societal implications point of view, this study will increase understanding of how society and patients can be affected by the new MDR and how these effects can be both positive and negative.

A limitation of the study is the lack of published literature related to clinical evaluation under the MDR. Future research opportunities would be to perform more qualitative studies within the device industry and among compliance stakeholders to understand the challenges to clinical evaluation under the MDR in more detail. However, this study is the first to investigate clinical evaluation in medical devices under the new EU regulations. This study will be a valuable source of information for academic teaching and understanding regulatory compliance, as well as for industry stakeholders to understand the requirements of the clinical evaluation process under the new MDR.

References

Baines, R., Hoogendoorn, P., Stevens, S., Chatterjee, A., Ashall-Payne, L., Andrews, T. and Leigh, S. (2022), "Navigating medical device certification: a qualitative exploration of barriers and enablers amongst innovators, notified bodies and other stakeholders", *Therapeutic Innovation and Regulatory Science*, Vol. 57 No. 2, doi: 10.1007/s43441-022-00463-4.

Behan, R., Pandit, A. and Watson, M. (2017), "New EU medical device regulations: impact on the MedTech sector", *Medical Writing, European Medical Writers Association (EMWA)*, Vol. 26, pp. 20-24.

Ben-Menahem, S., Nistor, R., Macia, G., Krogh, G. and Goldhahn, J. (2020), "How the new European regulation on medical devices will affect innovation", *Nature Biomedical Engineering*, Vol. 4 No. 6, pp. 585-590, doi: 10.1038/s41551-020-0541-x.

Berensmann, M. and Gratzfeld, M. (2018), "Requirements for CE-marking of apps and wearables", *Bundesgesundheitsblatt – Gesundheitsforschung – Gesundheitsschutz*, Vol. 61 No. 3, pp. 314-320, doi: 10.1007/s00103-018-2694-2.

Bianchini, E. and Mayer, C.C. (2022), "Medical device regulation: should we care about it?", *Artery Research*, Vol. 28 No. 2, pp. 55-60, doi: 10.1007/s44200-022-00014-0.

Burri, K.G. and Spoerri, A. (2020), "The value of registry data in the clinical evaluation of medical devices", *Medical Writing, European Medical Writers Association (EMWA)*, Vol. 29, pp. 16-21.

Byrne, R. (2024), "Medical device regulation in Europe – what is changing and how can I become more involved?", *EuroIntervention*, Vol. 15 No. 8, pp. 647-649, doi: 10.4244/EIJV15I8A118.

Carl, A.-K. and Hochmann, D. (2023), "Impact of the new European medical device regulation: a two-year comparison", doi: 10.1515/bmt-2023-0325.

Cohen, D. (2012), "How safe are metal-on-metal hip implants?", *BMJ*, Vol. 344, p. e1410.

Cohen, D. and Billingsley, M. (2011), "Europeans are left to their own devices", *BMJ*, Vol. 342, p. d2748, doi: 10.1136/bmj.-d2748.

Dezi, L., Battisti, E., Ferraris, A. and Papa, A. (2018), "The link between mergers and acquisitions and innovation", *Management Research Review*, Vol. 41 No. 6, pp. 716-752, doi: 10.1108/MRR-07-2017-0213.

Egbosimba, D. (2019), "Medical devices industry: the problem of clinical evaluation reports", *Annales de Biologie Clinique*, Vol. 77 No. 5, pp. 514-516, doi: 10.1684/abc.2019.1473.

European Commission (2016), "Tissues and cells", Public Health – European Commission, Text, 25 November, available at: https://ec.europa.eu/health/blood_tissues_organs/tissues_en (accessed 28 June 2021).

European Commission (2022), "New EU rules to ensure safety of medical devices", European Commission – European Commission, Text, available at: https://ec.europa.eu/commission/presscorner/detail/et/MEMO_17_848 (accessed 19 January 2023).

Fick, M. (2022), "Exclusive: EU to propose delay to medical device law amid supply worries", Reuters, 8 December.

Fraser, A.G., Nelissen, R.G.H.H., Kjærsgaard-Andersen, P., Szymański, P., Melvin, T. and Piscoi, P. (2021), "Improved clinical investigation and evaluation of high-risk medical devices: the rationale and objectives of CORE–MD (Coordinating Research and Evidence for Medical Devices)", *EFORT Open Reviews, the British Editorial Society of Bone and Joint Surgery*, Vol. 6 No. 10, pp. 839-849, doi: 10.1302/2058-5241.6.210081.

Garzotto, F., Comoretto, R.I., Dorigo, L., Gregori, D., Zotti, A., Meneghesso, G., Gerosa, G. and Bonin, M. (2022), "Preparing healthcare, academic institutions, and notified bodies for their involvement in the innovation of medical devices under the new European regulation", *Expert Review of Medical Devices*, Vol. 19 No. 8, pp. 613-621, doi: 10.1080/17434440.2022.2118046.

Guerlich, K., Patro-Golab, B., Barnacle, A., Baumann, U., Eicken, A., Fraser, A.G., Gruszfeld, D., Haas, N.A., Jonker, A.H., Kammermeier, M. and Kenny, D. (2023), "European expert recommendations on clinical investigation and evaluation of high-risk medical devices for children", *Acta Paediatrica*, Vol. 112 No. 11, pp. 2440-2448, doi: 10.1111/apa.16919.

Holborow, R. (2021), "Common regulatory gaps in clinical evaluation reports for medical devices and the pathway towards EU MDR transition", *Journal of Medical Device Regulation*, Vol. 18 No. 1, pp. 33-47.

Holborow, R. (2022), "Article 61(6) & MDCG 2020-6 clinical masterclass – well established technologies".

HPRA (2024), "MDR transitional provisions", available at: www.hpra.ie/homepage/medical-devices/regulatory-information/medical-devices-regulation/mdr-transitional-provisions (accessed 7 February 2024).

Hwang, T.J., Sokolov, E., Franklin, J.M. and Kesselheim, A.S. (2016), "Comparison of rates of safety issues and reporting of trial outcomes for medical devices approved in the European Union and United States: cohort study", *BMJ*, Vol. 353, p. i3323.

Ivanov, D., Dolgui, A., Das, A. and Sokolov, B. (2019), "Digital supply chain twins: managing the ripple effect, resilience, and disruption risks by data-driven optimization, simulation, and visibility", in Ivanov, D., Dolgui, A. and Sokolov, B. (Eds), *Handbook of Ripple Effects in the Supply Chain*, Vol. 276, pp. 309-332, doi: 10.1007/978-3-030-14302-2_15.

Johnson, C., McCaney, J., Ulme, K., Eichelberger, M., Lawyer, P., Tommer, G. and Rosenberg, B. (2022), "For cutting-edge innovations, the US pulls ahead of the EU in medtech regulation", *BCG Global*, 10 March, available at: www.bcg.com/publications/2022/us-ahead-in-medtech-regulation (accessed 12 December 2022).

Kearney, B. and McDermott, O. (2023a), "Challenges faced by manufacturers with clinical evaluation under the new European medical device regulations", *Cogent Engineering, Cogent OA*, Vol. 10 No. 2, p. 2261236, doi: 10.1080/23311916.2023.2261236.

Kearney, B. and McDermott, O. (2023b), "The challenges for manufacturers of the increased clinical evaluation in the European medical device regulations: a quantitative study", *Therapeutic Innovation and Regulatory Science*, Vol. 57 No. 4, pp. 1-14.

Kitchenham, B. (2004), *Procedures for Performing Systematic Reviews*, Keele University, Keele, Vol. 33, pp. 1-26.

Klonoff, D.C. (2020), "The expanding role of real-world evidence trials in health care decision making", *Journal of Diabetes Science and Technology*, Vol. 14 No. 1, pp. 174-179.

McDermott, O. and Kearney, B. (2023), "The value of using real-world evidence as a source of clinical evidence in the European medical device regulations: a mixed methods study", *Expert Review of Medical Devices*, Vol. 21 Nos 1/2, pp. 1-15.

Madanaguli, A., Srivastava, S., Ferraris, A. and Dhir, A. (2022), "Corporate social responsibility and sustainability in the tourism sector: a systematic literature review and future outlook", *Sustainable Development*, Vol. 30 No. 3, pp. 447-461, doi: 10.1002/sd.2258.

Majety, R.P.D., Katru, S., Veluchuri, J.P. and Juturi, R.K.R. (2021), "New era in medical device regulations in the European Union", *Pharm Regul Aff*, Vol. 10, p. 2.

Makower, J., Meer, A. and Denend, L. (2010), "FDA impact on US medical technology innovation".

Malvehy, J., Ginsberg, R., Sampietro-Colom, L., Ficapal, J., Combalia, M. and Svedenhag, P. (2022), "New regulation of medical devices in the EU: impact in dermatology", *Journal of the European Academy of Dermatology and Venereology*, Vol. 36 No. 3, pp. 360-364, doi: 10.1111/jdv.17830.

Medical Device Coordination Group (2020), "MDCG 2020-6 - Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under directives 93/42/EEC or 90/385/EEC a guide for manufacturers and notified bodies", April.

Medical Device Coordination Group (2021), "Guidance – MDCG endorsed documents and other guidance", available at: https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en (accessed 12 January 2023).

Medtech Europe (2021), "MedTech Europe's Facts and Figures 2021", MedTech Europe, available at: www.medtecheurope.org/resource-library/medtech-europes-facts-and-figures-2021/ (accessed 30 June 2021).

Melvin, T. (2022), "The European medical device regulation–what biomedical engineers need to know", *IEEE Journal of Translational Engineering in Health and Medicine*, Vol. 10, pp. 1-5, doi: 10.1109/JTEHM.2022.3194415.

Melvin, T. and Torre, M. (2019), "New medical device regulations: the regulator's view", *EFORT Open Reviews*, Vol. 4 No. 6, pp. 351-356, doi: 10.1302/2058-5241.4.180061.

Melvin, T., Kenny, D., Gewillig, M. and Fraser, A.G. (2023), "Orphan medical devices and pediatric cardiology – what interventionists in Europe need to know, and what needs to be done", *Pediatric Cardiology*, Vol. 44 No. 2, pp. 271-279, doi: 10.1007/s00246-022-03029-1.

Migliore, A. (2017), "On the new regulation of medical devices in Europe", *Expert Review of Medical Devices*, Vol. 14 No. 12, pp. 921-923, doi: 10.1080/17434440.2017.1407648.

Niemiec, E. (2022), "Will the EU medical device regulation help to improve the safety and performance of medical AI devices?", *Digital Health*, Vol. 8, p. 20552076221089079, doi: 10.1177/20552076221089079.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E. and Chou, R. (2021), "The PRISMA 2020 statement: an updated guideline for reporting systematic reviews", *Systematic Reviews*, Vol. 10 No. 1, p. 89, doi: 10.1186/s13643-021-01626-4.

Pandey, N., Nayal, P. and Rathore, A.S. (2020), "Digital marketing for B2B organizations: structured literature review and future research directions", *Journal of Business and Industrial Marketing*, Vol. 35 No. 7, pp. 1191-1204, doi: 10.1108/JBIM-06-2019-0283.

Pelayo, S., Marcilly, R. and Bellandi, T. (2021), "Human factors engineering for medical devices: European regulation and current issues", *International Journal for Quality in Health Care*, Vol. 33 No. 1, pp. 31-36, doi: 10.1093/intqhc/mzaa103.

Pongiglione, B., Torbica, A., Blommestein, H., De Groot, S., Ciani, O., Walker, S., Dams, F., *et al.* (2021), "Do existing real-world data sources generate suitable evidence for the HTA of medical devices in Europe? Mapping and critical appraisal", *International Journal of Technology Assessment in Health Care*, Vol. 37 No. 1, p. e62.

Pritchard, G. (2022), "Clinical evaluation reports: 6 years after the introduction of MEDDEV 2.7/1 revision 4", *Medical Writing, European Medical Writers Association (EMWA)*, Vol. 31, pp. 40-43, available at: 10/clinical-evaluation-reports-6-years-after-meddev-27_1-revision-4.pdf

Sorenson, C. and Drummond, M. (2014), "Improving medical device regulation: the United States and Europe in perspective", *The Milbank Quarterly*, Vol. 92 No. 1, pp. 114-150, doi: 10.1111/1468-0009.12043.

Stern, A.D. (2017), "Innovation under regulatory uncertainty: evidence from medical technology", *Journal of Public Economics*, Vol. 145, pp. 181-200.

Tarricone, R., Boscolo, P.R. and Armeni, P. (2016), "What type of clinical evidence is needed to assess medical devices?", *European Respiratory Review*, Vol. 25 No. 141, pp. 259-265.

Taylor, N.P. (2022), "EU health commissioner proposes MDR delay to prevent medical device shortages", *MedTech Dive*, available at: www.medtechdive.com/news/eu-mdr-delay-device-shortage/638491/ (accessed 12 December 2022).

Tranfield, D., Denyer, D. and Smart, P. (2003), "Towards a methodology for developing evidence-Informed management knowledge by means of systematic review", *British Journal of Management*, Vol. 14 No. 3, pp. 207-222, doi: 10.1111/1467-8551.00375.

Valla, B. (2021), "Common regulatory gaps in clinical evaluation reports for medical devices and the pathway towards EU MDR transition", *Journal of Medical Device Regulation*, Vol. 18 No. 4, pp. 1-14.

Vasiljeva, K., van Duren, B.H. and Pandit, H. (2020), "Changing device regulations in the European Union: impact on research, innovation and clinical practice", *Indian Journal of Orthopaedics*, Vol. 54 No. 2, pp. 123-129.

Wong, G., Greenhalgh, T., Westhorp, G., Buckingham, J. and Pawson, R. (2013), "RAMESES publication standards: meta-narrative reviews", *Journal of Advanced Nursing*, Vol. 69 No. 5, pp. 987-1004, doi: 10.1111/jan.12092.

Further reading

Bender, N., Portmann, M., Heg, Z., Hofmann, K., Zwahlen, M. and Egger, M. (2014), "Fish or n3-PUFA intake and body composition: a systematic review and meta-analysis", *Obesity Reviews*, Vol. 15 No. 8, pp. 657-665, doi: 10.1111/obr.12189.

Johnson, S. (2019), "Quality 4.0: a trend within a trend - ProQuest", *Quality*, Vol. 58 No. 2, pp. 21-23.

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