CORE-MD

Coordinating Research and Evidence for Medical Devices

Report on conditions on certificates by notified bodies

Deliverable 3.3

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Acronyms and abbreviations

AEG	Access with Evidence Generation
AETSA	Área de Evaluación de Tecnologías Sanitarias de Andalucía /Andalusian Health Technology Assessment Unit
AHRQ	Agency for Healthcare Research and Quality
IMDD	The Active Implantable Medical Devices Directive
ANVISA	National Health Surveillance Agency under The Ministry of Health
AOANJRR	Australian Orthopaedic Association National Joint Replacement Registry
ARTG	Australian Register of Therapeutic Goods
ASTER-D	Adverse Event Triggered Reporting for Devices
BSBC	Blue Cross and Blue Shield
BMJ	British Medical Journal
CADTH	Canadian Agency for Drugs and Technologies in Health
CAHR	Canadian Association of Health care Reimbursement
CEAR	Clinical Evaluation Assessment Report
CECP	Clinical Evaluation Consultation Procedure
CED	Coverage with Evidence Development
CE mark	European Conformity mark / *<<Conformité Européenne>>*
CFDA	China Food and Drug Administration
CMS	Centers for Medicare and Medicare Services
COFEPRIS	The Federal Commission for Protection Against Sanitary Risks
CORE-MD	Coordinating Research and Evidence for Medical Devices
CVZ	College voor zorverzekeringen
DELTA	Data Extraction and Longitudinal Trend Analysis
EAEU	The Eurasian Economic Union
ECRI	European Credit Research Institute
EU	European Union
EUDAMED	European Databank on Medical devices
EUnetHTA	European network for HTA
EUREQUO	European Registry of Quality Outcomes for Cataract and Refractive Surgery
FAMHP	Federal Agency for Medicines and Health Products
FDA	The U.S. Food and Drug Administration
FSCA	Field Safety Corrective Action
GHTF	Global Harmonization Task Force
HDE	Humanitarian Device Exemption
HHS	Health and Human Services
HRMD	High Risk Medical Devices
HTA	Health Technology Assessment

HTAi	HTA International
ICD	International Classification of Diseases
IDE	Investigational Device Exemption
IMDRF	The International Medical Device Regulators Forum
INAHTA	The International Network of Agencies for Health Technology Assessment
INMETRO	National Institute of Metrology, Quality, and Technology
IQWIG	Institute for Quality and Efficiency in Healthcare
INVIMA	National Food and Drug Surveillance Institute
LBI	Ludwig Boltzmann Institute for HTA
MDD	The Medical Device Directive
MDR	Medical Devices Regulation
MEDEVIPAS	MEdical DEvices VIgilance and Patient Safety
MedSun	Medical Product Safety Networks
MERCOSUR	Southern Common Market
MoH	Ministry of Health
MSAC	Medical Services Advisory Committee
NBs	Notified Bodies
NCDR	National Cardiovascular Data Registry
NEISS	National Electronic Injury Surveillance System
NEJM	New England Journal of Medicine
NEST	Systematized Nomenclature of Medicine-Clinical Terms
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NOC	Notice of Compliance
PCORI Horizon Scanning	Patient-Centered Outcomes Research Institute Horizon Scanning
PMA	Pre-Market Approval Letter
PMCF	Post-Market Clinical Follow-up
PMDA	Pharmaceutical and Medical Devices Agency
PRISMA	Preferred Reporting Items for Systematic reviews and Meta- Analyses
PSUR	Periodic Safety Update Report
RCT	Randomized Controlled Trial
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SNOMED-CT	Systematized Nomenclature of Medicine- Clinical Terms
TGA	The Therapeutic Goods Administration
TPD	The Therapeutic Products Directorate
TPLC	Total Product Life Cycle

UDI	Unique Device Identifier
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WoS	Web of Science

Table of Contents

Executive Summary 9
1. Introduction 11
1.1. Deliverable structure 15
2. Objectives 16
3. Methods 17
3.1 Methods for the Systematic Review 17
3.1.1 PICO's questions 17
3.1.2 Selection criteria 17
3.1.3 18
Study selection 18
3.1.4 18
Data sources 18
3.1.5 Data synthesis 20
3.2 Methods for the Survey of Notified Bodies experiences 20
4. Results 23
4.1 Results from Systematic Review 23
4.2 Results from Survey of Notified Bodies experiences 47
5. Discussion 50
5.1 Premarket entry for Medical Devices 50
5.2 Overview 51
5.3 Medical Devices Classification 52
5.4 Post-marketing evidence generation: lessons for High-Risk Medical Devices 52
6. Summary and conclusions 56
Limitations 57
References 58
Appendices 66

Index of figures

Figure 1. PRISMA flowchart from selected studies and other sources 24

Index of tables

Table 1. Description of included studies.....33
Table 2. Post-market reporting activities: Main outcomes 36
Table 3. Results of the Survey of Notified Bodies experiences: Medical Device Regulation of high-risk devices.....48
Table 4. Appendix 3: Mapping of regulatory frameworks, regulatory bodies, and HTA bodies worldwide and their role in the access pathway for medical devices.....84

Executive Summary

In this report, we present the results of the work done in task 3.3 (titled 'Report on conditions of certificates of notified bodies'), within Work package 3 (titled 'Clinical evidence generation after market access') of the CORE-MD project.

Work package 3 of the CORE-MD project has been divided into three tasks (Tasks 3.1 to 3.3), and aims to review and develop methods for aggregating data, develop a web-based tool to automate the surveillance of reports related to specific types of devices, and assess how the regulation for high-risk medical devices (HRMD) approaches post-approval evidence development schemes in Europe.

Task 3.3 is dedicated to study how post-market clinical evidence is generated for HRMD, based on an analysis of Notified bodies'(NBs) practices in applying conditions to certificates of conformity. Our aim was to describe the key aspects that NBs take into consideration related to the conditions and limitations applied to certificates of conformity, systematically reviewing the evidence collected about existing post-market evidence development schemes applied to HRMD, which should be generated according to the limitations applied to certificates of conformity. Additionally, we analyze similar regulations worldwide, focusing on post-approval evidence development schemes, to extract lessons that might be applicable to the European regulatory environment for high-risk medical devices.

Methods

The protocol of the methodology used for the systematic review search has been published (Appendix 1: Prospero's CRD 42023431233).

The aim of this deliverable is to provide the information extracted from the NBs survey, selected peer-reviewed publications and gray literature about post-market requirements and practices (e.g., the use of conditions applied to certificates of conformity) established for safety and surveillance on HRMD in Europe, extracting useful lessons from other jurisdictions too.

Results

The systematic review included 7 selected articles. No articles discussed conditions or restrictions on certificates imposed on HRMD by regulatory bodies, which was the primary objective of our review. 5 articles discussed other aspects of the regulatory system for approval or surveillance of HRMD in various jurisdictions. 2 articles discussed coverage with evidence development (CED) restrictions imposed on HRMD by national health technology assessment (HTA) authorities. The survey obtained responses from 13 NB. Of these, very few were able to provide data on the number of certificates issues, the number of rejections, and the number of certificates issued with restrictions or conditions. From those NB that did state that they issued certification with restrictions, these were imposed in the following areas: adhesion barrier, implantable suture, dermal filler, surgical mesh, implantable glucose sensor, leadless pacemaker and implantable brachytherapy seed for treatment of pancreatic cancer. With regard to the nature of the

restrictions or limitations, four of the certificates were issued with a restriction on their intended purpose and three restrictions were associated to the novelty of the medical device indicated in the regulatory application, and to concerns related to the safety and performance of the device, with instructions to undertake a PMCF study (for details see Table 3).

Conclusions

The possibility for NBs to impose limitations on certificates of conformity is contemplated in the new European regulation for medical devices, but this pathway is not sufficiently developed, which has led to this option barely being used in practice. Several national HTA agencies are using or considering CED schemes.

1. Introduction

The regulation for medical devices has traditionally not been as strict as regulatory requirements for medicines, which caused concerns over the safety of devices in the past (1). The EU introduced a new Medical Device Regulation (MDR [2017/745]) to impose higher requirements for medical devices, at premarketing testing, certification and post-marketing surveillance (2).

In this context, the European Commission Horizon 2020 Program awarded a research grant to the CORE-MD project, launched in April 2021, to strengthen the methodological and knowledge base supporting the implementation of the new regulation. *The project has several aims*. These include translating expert scientific and clinical evidence on study designs for evaluating HRMD into advice for EU regulators. Additionally, it seeks to propose how new trial designs can contribute and suggest ways to aggregate real-world data from medical device registries. Furthermore, the project aims to build capacity through activities such as conducting multidisciplinary workshops. These workshops are intended to propose a hierarchy of levels of evidence from clinical investigations, as well as educational and training objectives for all stakeholders. The overarching goal is to build expertise in regulatory science in Europe.

Medical devices are a broad category of products and equipment designed for medical purposes. According to the WHO's (World Health Organization) definition, a medical device is "an article, instrument, apparatus or machine that is used in the prevention, diagnosis or treatment of illness or disease, or for detecting, measuring, restoring, correcting or modifying the structure or function of the body for some health purpose" (3).

With regard to health products, these have been regulated in the past by three Directives in the European Union (EU), as follows: The Active Implantable Medical Devices Directive (AIMDD) 90/385/EC(4), the Medical Device Directive (MDD,93/42/EEC)(5) and European Directive (IVDD, 98/79/EC 98/79/EC)(6). These directives should have been transposed into individual members' regulations. Nevertheless, because of the fast advance in new technologies development and their possible effects in individual patients' state of health, there were some international acts aimed to standardize as maximum as possible the characteristics and assumptions related to the lifecycle of health technologies (Assessment, Surveillance, Safety…). Giving place to different relevant measures as: the International Medical Device Regulators Forum (IMDRF), The Global Harmonization Task Force (GHTF), or the new European Regulation (EU)(MDR 2017/745) of the European Parliament and of the council of 5 April 2017 on medical devices(2,7,8).

In agreement with the actual European regulation (2) medical devices are classified according to the level of risk: class I (low), class IIa (medium) and classes IIb and III (high). The main focus of CORE-MD is on high-risk medical devices. They are a class of medical device that, to access healthcare markets, need to complete multiple steps of evidence generation and evaluation, including the preparation of sufficient evidence to prove their quality, safety and efficacy to meet regulatory standards, and evidence to show their additional relative efficacy and value for money, in response to the requirements of HTA agencies

(9). Post-market evidence generation studies are relevant to fill evidence gaps to answer questions asked both by regulators as well as by HTA bodies (10).

The responsibility over the authorization of a new medical device entering the market is decentralized, and corresponds to 'independent conformity' assessment organizations called NBs (11). The evidence requirements at the different stages of the lifecycle of a HRMD have been described and grouped in phases focused in pre-market (pre-clinical research/1); Discovery and Ideation; 2); Invention and prototyping; 3)Development) and entry market (Preclinical research and beginnings clinical research/3)Development; 4)Consolidated use) generating as a consequence that Surveillance and Safety Post-market evidence (Clinical research/4)Consolidated use &; 5)Obsolescence & replacement) kept poorly developed or unexploited (12,13). NBs autonomous third-party organizations designated by EU Member States to assess and verify medical devices' conformity with regulatory standards) are responsible for enacting the regulation for medical devices in the EU. International organizations, such as the WHO and the International Medical Device Regulators Forum (IMDRF), have published reports to try and offer guidance to regulators dealing with the challenges associated to the regulation and post-market evidence surveillance for medical devices (14,15).

Central to the transition from the MDD to the MDR is the role of NBs that play a pivotal role in the certification process, ensuring that high-risk devices adhere to rigorous safety and performance criteria (16). The transition from the MDD to the MDR also significantly amplifies the role of NBs—under the MDD, NBs played a central role in evaluating high-risk devices and granting CE (Conformité Européenne) marks, indicating conformity with EU safety and performance standards; after the implementation of the new MDR, NBs continue to play a pivotal role, but the regulation imposes more rigorous requirements on new medical devices, with the weight that gives to NBs, which will be the judges applying a more demanding regulation (17). Under the new MDR, an opinion of the Expert Panels will be considered on the manufacturer Clinical Evaluation Assessment Report (CEAR) and NBs' Clinical Evaluation Consultation Procedure (CECP) (2,18,19). They are entrusted with assessing the conformity of HRMD against heightened safety and performance standards, and their oversight extends to post-market surveillance. Their role in evaluating clinical data and conducting rigorous inspections is more pronounced, reflecting the increased scrutiny placed on HRMD (2).

Clinical evidence for new HRMD is often limited at the time when a first regulatory decision needs to be made, highlighting the crucial role of post-approval evidence in guiding decisions throughout a product's lifecycle. This stands in contrast to pharmaceuticals, where the European Medicines Agency (EMA) and similar agencies worldwide (20) often require extensive pre-market clinical trials. In the case of medical devices, the regulatory landscape varies, relying more on post-market evidence. Conditional approval of drugs in Europe is a regulatory pathway established by the EMA to provide access to medicines that address unmet medical needs, subject to the marketing authorization holder collecting the necessary evidence to mitigate the key sources of uncertainty identified. This approach allows promising drugs to receive approval based on limited clinical data, particularly in cases where the benefits of the drug outweigh potential risks. EMA grants conditional marketing authorization when there is a clear need for

a treatment, such as during public health emergencies like the COVID-19 pandemic.

The Certificate of Conformity, issued by NBs, serves as evidence of a medical device's compliance with the MDR. For high-risk devices, obtaining this certificate necessitates a scrupulous and comprehensive process that includes exhaustive clinical evaluations, risk assessments, and continuous post-market surveillance. When high-risk devices are needed but clinical evidence is scarce, there may be circumstances when NBs can grant certificates of conformity but with prescribed conditions. The MDR does not explicitly mention terms like 'conditional certification'. It does, however, outline the possibility for NBs to grant certificates with particular conditions or limitations (11). Annex VII, specifically section 4.8 titled 'Decisions and Certifications,' contains relevant details regarding the decision-making process of NBs when they consider issuing certificates with conditions, limitations, or provisions (21). Restrictions and limitations might include advice to the manufacturer to restrict the intended purpose of the device to certain groups of patients or certain medical indications, impose a limit on the duration of validity of the certificate, an instruction to undertake specific post-market clinical follow-up (PMCF) studies, impose other restrictions in its conformity assessment report, as appropriate (MDR Article 56.3; (Annex IX)) (2).

In addition, a requirement in the new regulation is that derived information from post-market HRMD should be stored in databases to promote an easier and standardized recollection of HRMD data, as it is expected to happen with EUDAMED (European Databank on Medical devices) in EU countries (14,22). Among the different common activities derived from the standardization process of safety and surveillance in the world, one of the most tangible was the use of a Unique Device Identifier (UDI) system (23). This tool would be able to record medical devices data referred to named Field Safety Corrective Actions (FSCA) employed in the principal worldwide powers like: The United States of America (USA), the Euro-Asian Economic Union (EAEU), Southern Common Market (MERCOSUR); and Periodic Safety Update Report (PSURs), in EU cases (2,13,23,24).

With respect to Surveillance and post-market HRMD databases, the FSCA should be submitted into these mentioned platforms (e.g.: EUDAMED, U.S. FDA, HELENA, etc.) as part of Postmarket Clinical Follow-up (PMCF), a proactive process that collects and evaluates clinical data on the safety and performance of a medical device in normal use. However, this information is difficult to obtain given that individual regulatory bodies from each country input data in their local languages. Such difficulty in obtaining post-market data has raised concerns about how the standard procedure of post-market safety surveillance carried out for HRMD to maintain their “Certificates of conformity” is done in the EU.

The aims of this report are to analyze the landscape of post-market and surveillance requirements and practices (e.g., the use of conditions applied to certificates of conformity) to ensure the continued safety, quality and efficacy of HRMD in Europe, extracting useful lessons from other jurisdictions too.

To achieve those aims, firstly, we reviewed the literature related to post-approval evidence development schemes for high-risk medical devices and extend and update earlier analyses in order to identify and

synthesize how schemes are operated worldwide, drawing lessons from the experience of other regulators, and from the European Medicines Agency (EMA).

Secondly, we present the results of a survey we conducted to illustrate the main topics considered by the NBs in terms of conditions and limitations imposed on certificates of conformity for HRMD, applicable on the EU market. These types of products need a previous evaluation by the NBs which allow them to obtain the CE mark (2), a *sine qua non* aspect for free market circulation in EU countries.

1.1. Deliverable structure

This report introduces the state of the art for the regulatory assessment of the safety and efficacy of HRMD, how these aspects are evaluated in Europe and Worldwide, specifically focusing on the restrictions and limitations imposed on certificates by the competent authorities in each country and according to their corresponding legislation and regulatory bodies.

In order to perform this report, AETSA and the UGR have performed a systematic review of post-market evidence development schemes, how they are applied in the regulatory EU system, comparing the process described with the approaches applied to regulatory post-market evidence generation requirements in different entities and institutions in different parts of the world.

The protocol underpinning our systematic review was published (See Appendix 1: Prospero's CRD 42023431233) and a search strategy was developed to obtain the sample of selected studies. Once data were identified in research articles and reports, results were summarized in tables and in a descriptive text. To support the information derived from this research, we conducted a survey which was employed to ask for NB's about how conditions to certificates are applied, the follow-up conducted in instances when conditions to certificates are applied and any downstream consequences derived from the new evidence collected.

The results were discussed with the available bibliography according to the methodological structure explained in this report. Finally, a series of conclusions were provided.

Additional and complementary information were provided in appendices (Appendix 2-5).

2. Objectives

The objective of Task 3.3 were twofold:

a) To review the literature related to post-approval evidence development schemes applied in regulatory systems for high-risk medical devices/HRMD.

b) To generate evidence, through a survey, that helps us understand how decisions are made by NBs to apply restrictions and limits to certificates of conformity for high-risk medical devices, and to understand the challenges that the new regulation poses to NBs, with particular emphasis on the application of restrictions and limits to certificates of conformity for high-risk medical devices.

3. Methods

In the context of an EU-funded CORE-MD (Coordinating Research and Evidence for Medical Devices) project (25), a systematic review was conducted following the published PROSPERO's protocol (CRD42023431233 - Refer to Appendix 1; available as well on https://www.core-md.eu/library/). This Review was conducted according to the PRISMA guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (26)and it is available in full on the CORE-MD website (https://www.core-md.eu/library/) (25).

We also carried out a survey to NBs asking them questions seeking to generate evidence that help us understand how decisions are made by NBs to apply restrictions and limits to certificates of conformity for high-risk medical devices, and the challenges they face in doing so (further details describing the methods applied on this survey are reported in sub-section 3.1.5, below).

3.1 Methods for the Systematic Review

3.1.1 PICO's questions

This review will examine how evidence development schemes are established in order to evaluate the post-market lifecycle stage of HRMD. According to this, we proposed the following PICO's question:

P (Population): HRMD (Class IIb - surgically invasive or active devices partially or completely implanted into the body, and even modify the body's composition fluids; Class III - devices directly connected to blood circulatory system or central nervous system and/or devices which contains a drug). MDR-Article 51-Classification of devices. (25)

I (Intervention): Different types of post-approval/post-market development schemes for HRMD (Class III and implantable; MDR – Article 51) in different regulatory jurisdictions.

C (Comparator): Given the focus of the study, it was not considered.

O (Outcome): Report on conditions/requirements for conformity assessments that lead to further evidence generation and post-market surveillance for HRMD in different countries.

3.1.2 Selection criteria

A search strategy was developed (See Appendix 2: Search Strategies) according to the following selection criteria:

Inclusion criteria:

1. HRMD – class III and implantable:
    - Class IIB - Class IIb refers to most surgically invasive or active devices which are partially or completely implanted into the body. This class may also modify the composition of bodily

fluids.
- Class III – Devices directly connected to Circulatory or Central Nervous System or it contains drugs.
- MDR – Article 51 – Classification of devices (2).

2. Post-market evidence development schemes established by medical device regulatory authorities.
3. Regulation state.
4. Conditional approval/certificate of conformity/Restrictions or limitations.
5. Adverse event reporting schemes.

Exclusion criteria:

1. Non-human studies.
2. Pre-market evidence schemes.
3. HTA reports unless they address Conditional approval/certificate of conformity/Restrictions or limitations of HRMD.
4. Regulatory bodies from countries which do not template HRMD legislation.

Neither language nor date restrictions were established. Discrepancies were solved by team consensus. Documents were selected with regard to regulation from HRMD post-market evidence. The timeframe for our search was from 1st January to 27th September 2023.

3.1.3 Study selection

We included systematic reviews and relevant documents or reports from experts in Medical Device regulation. We also searched specific websites (HTA, Regulatory and Health agencies, MoH) to complement results from studies selected (See Appendix 3- Medical Devices Regulations, HTA bodies and other institutions worldwide with a mandate over medical devices). Zotero was employed as bibliographical reference manager (27).

In case of discrepancies, a third reviewer intervened to resolve any differences. An information specialist was responsible for formulating and executing the search strategy. Amstar-2 was employed as quality assessment tool for documents retrieved for our report (28), despite limitations some documents may present (see limitations, below) due to their belonging as HTA reports.

3.1.4 Data sources

According to the search strategy and Covidence PRISMA flow diagram (See Figure 1), the information sources were extracted from the following Databases:

- Medline (Ovid)
- Embase (Excerpta Medica DataBase)
- Cochrane Library (Cochrane Review Database)
- INAHTA (International HTA Database)
- WOS (SCI Science Citation Index)

In addition, we searched other relevant sources as international and national regulatory and HTA

agencies:

- National Institute for Health and Care Excellence (NICE)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Agency for Healthcare Research and Quality (AHRQ)
- European Credit Research Institute (ECRI)
- U.S. Food and Drug Administration (FDA)
- National Institute for Health and Care Research (NIHR)
- PCORI´s Horizon Scanning Database.
- Trip Medical Database

As Tarricone et al. (2014) described: "*Although the objectives of regulators and HTA bodies are, and must, remain distinct, it is also true that HTA is becoming a formal barrier to be overcome in many jurisdictions before a device can be adopted and diffused within the healthcare system. Manufacturers often need to develop clinical evidence for HTA bodies instead of regulators (i.e., in some European countries) or conversely for regulators and not for HTA bodies (i.e., the USA)".* Despite the nature of our task was focused on regulation, some HTA activities may be important to highlight in this task due to the impact of some HTA reports into policy and regulators decisions.

The following descriptors and key words were employed adapting the initial strategy to the syntax of each database: medical devices, prostheses, heath technology, device approval, evidence generation, condition approval, conformity certificate (see in detail in Appendix 2: Search Strategies). These searches were restricted by study type to systematic reviews and meta-analyses. There were no limitations based on language or date.

Additionally, we performed searches into regulatory bodies, HTA bodies and other institutions worldwide with a mandate over medical devices in order to complement data from selected studies (See Appendix 3: Medical Devices Regulations, HTA bodies and other institutions worldwide with a mandate over medical devices (Table 4)).

Due to the unknown evidence submitted for HRMDs already on the market, because of the confidential activities given among NBs and manufacturers in the case of EU, the research team decided to make a table based on the websites of entities related to HTA activities and organizations belonging to the European network for HTA (EUnetHTA) and to the INAHTA, and the website of the HTA International (HTAi) in order to establish a conceptual framework to explore the different regulatory bodies in worldwide countries and their actual regulations on medical devices (See Appendix 3: Medical Devices Regulations, HTA bodies and other institutions worldwide with a mandate over medical devices (Table 4)). The information retrieved from these countries was:

- Country name (EU member/Non-EU member)

- Medical Devices Regulation (MDR)
- MD's classification
- Regulatory Body
- Assessment comparing Surveillance/Safety
- HTA (Competent Authority)

In addition, data extracted from key documents was depicted in **Table 2 - Post-market reporting activities: Main outcomes** and **Table 3 - Results of the Survey of Notified Bodies experiences: Medical Device Regulation of high-risk devices** and includes the following information:

- Authors & date
- Study name
- Study design
- Amstar's Checklist classification
- Population
- Population size
- Databases & Search's timeline
- Objective/s
- Number of Countries & Jurisdictions
- Countries & Jurisdictions

3.1.5 Data synthesis

The extracted results were collected in evidence tables; a descriptive and narrative analysis was conducted, as well as a qualitative synthesis of the results based on the main outcome measures.

3.2 Methods for the Survey of Notified Bodies experiences

The CORE-MD survey was developed in the EU Survey tool (https://ec.europa.eu/eusurvey/home/welcome)(29). The questions contained in the survey, their format and content were designed after extensive consultations with experts from NBs, regulators and members of the CORE-MD consortium. It was designed in an anonymised summary format, so that requirements for confidentiality to manufacturers were respected.

The questionnaire was first designed as a prospective study with the main goal of prospectively collecting the experiences of NBs applying restrictions or limitations to certificates of conformity. The questionnaire contained 29 questions organised into 4 sections (Appendix 4):

I. Attributes of the NB evaluating the device - general information about the NB e.g. number of staff or location, engagement of external experts;

II. Attributes of the device - information regarding indication and patient population;

III. Evidence submitted by manufacturer (study design, inclusion of control group, sample size, principal

end point of performance, study blinding, safety, length of follow-up);

IV. Overall analysis of conformity assessment of the device: cumulative evidence from all studies supporting the dossier, role and opinion of expert panel, and outcome of the conformity assessment;

Participants were asked to fill in one questionnaire per device and to submit information regarding evidence submitted by the manufacturer (Section III) of up to 5 studies of relevance.

The survey was distributed to NBs, members of Team-NB, in April 2022. However, despite repeated attempts to encourage NBs to take part in the survey, we only recorded 2 incomplete responses to the questionnaire.

From intensive interactions with NBs that collaborate with CORE-MD, regulators and members of the CORE-MD consortium we understood that the use of 'conditions' has in fact been quite limited or very restricted. That has made it very challenging to undertake a prospective study of the regulatory utility of 'conditions' under the new MDR, especially when the NBs were already more than fully occupied trying to recertify legacy medical devices for the MDR. As a result of these consultations the questionnaire has undergone significant changes on the survey scope, content and number of questions. Instead of doing a prospective study we decided to perform a retrospective study instead, with the goal of conducting a survey of NB decisions to investigate and provide insights into the way the MDDs had been applied and how the new regulation on MDs is working in Europe in practice. The final version of the survey was intended to give an insight into the “baseline” of how the system was functioning before the MDR was implemented in full, to understand the strengths of the new system early on and identify potential areas for further development.

The final questionnaire comprised four distinct inquiries (Appendix 5):

1. Determining the total number of certificates issued for class III and implantable medical devices under the MDD and Active Implantable Medical Device Directive (AIMDD) between August 1, 2012, and May 26, 2021.
2. Identifying the number of applications for certificates of class III and implantable medical devices that were rejected within the scope of the MDD and AIMDD between August 1, 2012, and May 26, 2021.
3. Quantifying the certificates issued for class III and implantable medical devices with associated restrictions and limitations in accordance with the MDD and AIMDD between August 1, 2012, and May 26, 2021.
4. Providing a comprehensive description of the device, its intended purpose, indications, and medical application area, while also detailing the nature of any restrictions or limitations imposed on the certificate. Respondents were guided to complete this question using a downloadable Word document. The information required to complete the document was as follows:
    - Medical devices where certificates with restrictions or limitations were issued
    - Intended purpose, indication and area of medicine
    - The nature of the restriction or limitation? e.g. (i) restrict the intended purpose of the device, (ii) impose a limit on the duration of validity of the certificate, (iii) limit the release of the device only to specific post-market clinical follow-up (PMCF) studies, (iv) other

The survey was distributed to NBs in March 2023, and responses were collected until September 2023. Initially, the questionnaire was disseminated to NBs through the coordinators of the European Association of NBs (Team-NB). Subsequently, direct contact was established with NBs based on the lists available on the NANDO website (New Approach Notified and Designated Organisations; https://webgate.ec.europa.eu/single-market-compliance-space/#/notified-bodies)(30). Members of NBs were provided with multiple options to participate in the survey: 1) to submit their responses online by completing the questionnaire on the EU Survey platform, 2) to take part in personal interviews, where a representative from our group aided in completing the questionnaire, 3) online meetings were arranged to address any potential concerns or questions related to the survey.

4. Results

In this section, we present the findings we extracted from the systematic review of the literature we performed (in sub-section 4.1 below) and the results of the survey (in sub-section 4.2 below).

4.1 Results from Systematic Review

In our review of the literature, two researchers (JAL & AD) carried out screening phase of 2069 studies from various registers (See **Figure 1 - Covidence PRISMA flow diagram**) by title and Abstract, the reviewers compared results and resolved any disagreements through dialogue. 30 Studies were selected for full text screening, 7(31–37) of them were selected for further analysis. The use of the AMSTAR-2 online checklist (https://amstar.ca/) to assess the quality of the studies showed that all of them displayed either low or critically low quality. In addition, one report was retrieved from the FDA to be included (38)**.** The selected articles' data were synthesized and structured in tables as seen in **Table 1 - Description of included studies** and **Table 2 - Post- market reporting activities: Main outcomes.**

Due to the heterogeneity of results from selected studies we performed a descriptive synthesis as follow:

Of the 7 studies that fulfilled the inclusion criteria, five were systematic reviews and two HTA reports (addressing issues related to conditional approval/certificate of conformity/Restrictions or limitations of HRMD). The included studies were published between 2009 and 2021. The authors provided information regarding the following countries or jurisdictions: EU (Netherlands, Germany, France, Belgium, Spain, Finland, Denmark, Italy, Latvia, Portugal, United Kingdom (UK)), USA, Australia, Canada, China, Japan, Brazil, Argentina, Colombia, Brazil and Mexico. In addition, **Table 1 – Description of included studies** outlines main objectives from each study, the data sources, the quality assessment score and other observations, highlighting their relevance to the objectives of this report, with regard to the belonging of the documents to Regulatory authorization and post marketing surveillance or HTA and/or Price & Reimbursement.

Key elements of post-marketing surveillance and vigilance activities in EU, USA, Canada, Australia, China, Japan and Brazil include adverse event reporting or vigilance reporting that relies on manufacturers, clinicians, and patients to report incidents. Main outcomes of post- market reporting activities in different jurisdictions worldwide are summarized in Table 2.

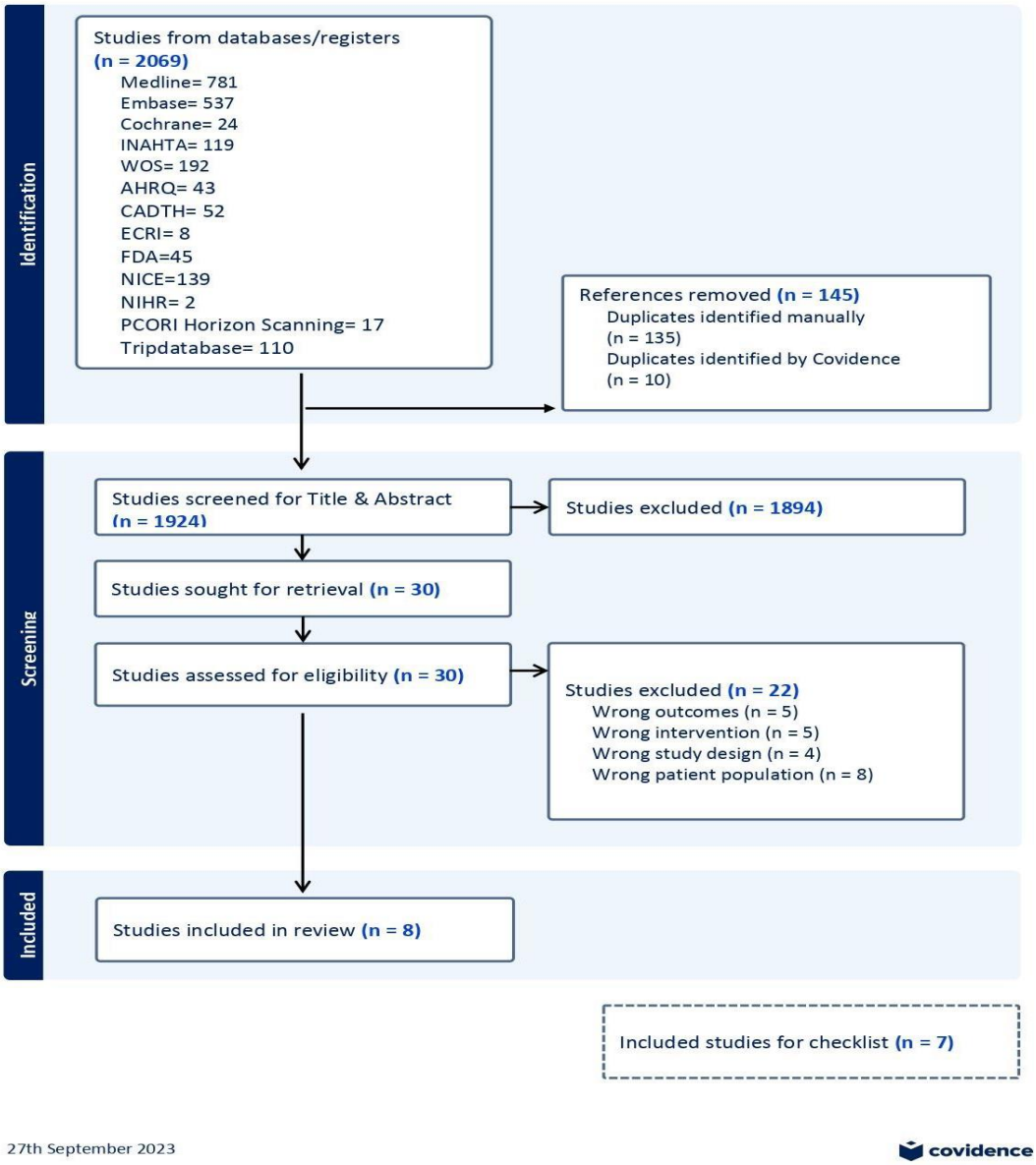

Figure 1. PRISMA flowchart from selected studies and other sources

Table 1. Description of included studies

Study	Population	Population Size	Databases & Search's Timeline	Objective/s	Countries or Jurisdictions -Nr-	Observations and Amstar-2's Quality Score
Tarricone *et al.* 2014(31)	Empirical articles and commentaries describing or discussing the regulatory framework for medical devices and the need for integration between existing regulatory, coverage and HTA processes.	50 Final studies included: - 30 full-text screened. - 20 editorial/Commentary search (n: BMJ=12 & NEJM=8).	• Pubmed • Ovid MEDLINE • EMBASE • EconLit • British Medical Journal (*BMJ*) • NEJM 2000-2014	Identify documents prescribing the processess for pre-market approval and post-market vigilance of medical devices.	USA EU Australia Canada China Japan Brazil -7-	Regulatory authorization and post marketing surveillance - Critically Low Quality Review
Rey-Ares *et al.* 2016(32)	Requirements for medical devices licensing and reimbursement in four Latin- American countries. One specific device was selected to describe its regulatory and coverage trajectory.	74 final studies included: - 12 studies from databases. - 62 publications from other sources.	• Pubmed • Lilacs • ISPOR Digest • Value in Health Regional Issues Journal • MoHs, HTA, regulatory and Health agencies specific websites (Other sources) No date restrictions till February 2015	To assess, describe and compare the requirements and pathways from licensing to coverage of the decision-making process used for medical devices in comparison to drugs in the Health systems of Argentina, Brazil, Colombia and Mexico.	Argentina Brazil Colombia Mexico -4-	Regulatory authorization and post marketing surveillance - Critically Low Quality Review
Reckers-Droog *et al.* 2020(33)	CED schemes for Medical Devices (MDs)	27 final studies included: - 6 reported on challenges with CED schemes in the specific context of MDs. - 21 on challenges with CED schemes in the context of different types of health technologies, including MDs.	• WoS • Pubmed (National Library of Medicine) • Embase • Scopus • Google • Google Scholar *in September 2018 & in January 2019	To identify and describe the challenges that payers and manufacturers might face when assessing the desirability of, choosing the research design for, implementing, and evaluating CED schemes for MDs.	USA EU (Netherlands, Germany, France, Belgium, Spain) Australia Canada -4 (8)-	HTA or Price & eimbursement schemes o mitigate uncertainty ter adoption in national health systems - Low Quality Review

Study	Population	Population Size	Databases & Search's Timeline	Objective/s	Countries or Jurisdictions -Nr-	Observations and Amstar-2's Quality Score
Pane *et al.* 2021(34)	Tools used for medical device safety signal detection	24 final studies included: - 11 review articles - 13 studies (12 retrospective studies and 1 prospective study). Twenty-one articles included information on post-market data sources of medical devices, 10 articles included information on signal detection methodologies for medical devices and 4 articles included information on coding dictionaries for medical devices.	• Embase • Medline • Cochrane • Web of Science • Google Scholar Jan-2004 through Jan-2017	To describe aspects that influence signal detection of safety issues related to medical devices in order to identify gaps and provide recommendations for optimizing signal detection approaches	USA Canada Brazil Japan Australia EU -6-	Regulatory authorization and post marketing surveillance - Low Quality Review
Krüger *et al.* 2013(35)	Authorization process and its associated evidence requirements for HRMD in the USA, Europe, Australia and Canada. (Seven high-risk devices for exemplary presentation)	45 final studies included: - 4 observational studies. - 12 Randomized Controlled Trials (RCTs) - 20 Case series - 1 report - 7 Expert opinions - 1 Systematic Literature Review	• Pubmed • Official reports from the relevant national regulatory bodies (except NBs): ✓ Centers for Medicare and Medicare Services (CMS) ✓ Aetna ✓ Blue Cross and Blue Shield (BSBC) ✓ United Healthcare ✓ Kaiser Permanente ✓ AHRQ ✓ College voor zorverzekeringen (CVZ) ✓ MDS, Federal Joint Committee (G-BA), ✓ Institute for Quality and Efficiency in Healthcare (IQWIG) ✓ NICE ✓ Ludwig Boltzmann Institute for HTA (LBI) ✓ Medical Services Advisory Committee (MSAC) ✓ Canadian Association of Health care Reimbursement (CAHR) ✓ No time period mentioned	Insight into four authorization systems evidence at time of approval and reimbursement. Objectives: - Authorization process in the four regions. - Evidence available at time of approval and reimbursement decision.	USA Europe (England, The Netherlands, Germany, Austria) Canada Australia -4 (8)-	Regulatory authorization and post marketing surveillance - Critically Low Quality Review

Study	Population	Population Size	Databases & Search's Timeline	Objective/s	Countries or Jurisdictions -Nr-	Observations and Amstar-2's Quality Score
Carbonneil *et al.* 2009(36)	Access with Evidence Generation (AEG) policies, particularly at the coverage decision stage	Not provided	• MEDLINE • BIOSIS Previews • Current Contents • EMBASE • INAHTA • DARE • Gray literature (reports on the Web sites of medicines agencies, HTA agencies and national health insurance bodies) Period: 1990–2008	To identify the AEG mechanisms implemented in various countries, to use them to draw up a common policy framework applicable at both the marketing approval and coverage decision stages To identify the key factors for its successful operation	Australia Canada EU (Belgium, Finland, Denmark, France, Germany, Italy, Latvia, Netherlands, Portugal, Spain, UK) USA -4 (14)-	HTA or Price & Reimbursement – Critically Low Quality Review
Baeyens *et al.* 2015(37)	HRMD (class III and implantable devices) after their CE-marking in Belgium	Not provided	• Belgian and European legal databases (BELGIQUELEX, EURLEX) • Communications, Guidelines and reports of the European Commission • Parliament and Council Parliamentary work of the European and national legislation • Position papers from professional and sectorial associations • Articles published in scientific or legal publications • Legal experts and lawyers from across Europe were consulted • Official websites and documentation from national health products and Reimbursement authorities in various European countries • Representative from the Belgian health product and reimbursement authorities (Federal Agency for Medicines and Health Products (FAMHP - fagg-afmps) and NIHDI), from manufacturers associations, and from • hospitals were consulted	The aims of this report were as follow: - Getting to know the existing legal opportunities in a selection of European's countries, including Belgium, to introduce a high-risk device on the market in a guided manner. - To identify the crucial legislation to apply one or more of the above identifies and new possibilities to have a guided introduction of CE labelled devices (which are not in conflict with European l - To investigate the possibility of a higher protection of the patients when certain CE marked HRMD are used (class III and implantable devices).		Critically Low Quality Review

Table 2. Post-market reporting activities: Main outcomes

Country or Jusrisdiction	Regulatory structures	Key elements of post-marketing surveillance & vigilance activities	Medical device registry
EU	Directive 90/385/EC, 93/42/EEC and 98/79/EC) (2,19). The conformity assessment procedure, with exception of low-risk devices, is carried out by third parties, called NBs, which are designated by the Member States Competent Authorities.	Adverse event reporting or vigilance reporting: MDD (Tarricone, *et al.*)(31): reporting by medical practitioners or medical institutions is encouraged but optional - Member States may or may not introduce this legal requirement in their national legislation MDR: adverse events and device deficiencies that occur during clinical investigations should be reported to the Member States in which those clinical investigations are being conducted and submit the reports to EUDAMED database	EUDAMED
USA	Title 21 of the Code of Federal Regulations - Food, Drug, and Cosmetic Act (FD&C Act); Medical Device Amendments Act (MDA) and the Bioterrorism Act. (39) The "Premarketing Notification" or 510(k) clearance procedure and the "Premarket Approval" (PMA) for HRMD, is carried out by the FDA.	Adverse event reporting or vigilance reporting: the manufacturer, distributor, competitor, healthcare providers and patients have the duty to report adverse events (Tarricone *et al.*) (31) (Title 21 of the Code of Federal Regulation, section 803) (39).	U.S. FDA // Medical Device Safety and Recalls Communications (See Appendix 3: Medical Devices Regulations, HTA bodies and other institutions worldwide with a mandate over medical devices (Table 4)).
Canada	The primary regulatory framework for medical devices in Canada is the Medical Devices Regulations (SOR/98- 282)(40) under the authority of the Food and Drugs Act. The regulatory oversight is provided by Health Canada, specifically the Medical Devices Directorate. Health Canada reviews medical devices to assess their safety, effectiveness and quality before being authorized for sale in Canada. The license (i.e., notice ofcompliance) is issued once all requirements are satisfied.	Adverse event reporting or vigilance reporting: No results retrieved, but according to the Medical Devices Regulations - SOR/98-282 (Section 81) (40), we can observe some examples: *(f) a risk assessment comprising an analysis and evaluation of the risks, and the risk reduction measures adopted for the purposes of conducting investigational testing of the device, including, as appropriate.* *(iii) information respecting any cautions, warnings, contra-indications and possible adverse effects associated with the use of the device;* *(v) in the event of an incident involving the device and that meets the following conditions, report the incident and the circumstances surrounding it to the Minister and to the manufacturer or importer of the device within 72 hours after the qualified investigator becomes aware of the incident:*	The Canada Vigilance Program (See Appendix 3: Medical Devices Regulations, HTA bodies and other institutions worldwide with a mandate over medical devices (Table 4)).

Country or Jusrisdiction	Regulatory structures	Key elements of post-marketing surveillance & vigilance activities	Medical device registry
		(A) the incident is related to a failure of the device or a deterioration in its effectiveness or any inadequacy in its labelling or in its directions for use, and *the incident has led to the death or a serious deterioration in the state of health of a patient, user or other person or could do so were the incident to recur.*	
Australia	The specific regulation for medical devices is found in the Therapeutic Goods Act 1989 and the Therapeutic Goods Regulations 1990(41). The TGA (Therapeutic Goods Administration) is responsible for evaluating and deciding the incorporation, monitoring and withdrawal of HRMD. The sponsor needs to demonstrate that the device complies with a set of '*Essential Principles*' for the quality, safety and performance of the medical devices.	Adverse event reporting or vigilance reporting: Manufacturers and sponsors are required to report certain types of adverse events associated with their medical devices to the TGA. Reporting by stakeholders' others than manufacturers is only encouraged (*Tarricone et al*.) (31).	Database of Adverse Event Notifications (DAEN) (See Appendix 3: Medical Devices Regulations, HTA bodies and other institutions worldwide with a mandate over medical devices (Table 4))
China	Regulations on the Supervision and Administration of Medical Devices (Order No. 739) of 9 February, 2021(42). The National Medical Products Administration (NMPA), previously named CFDA (China Food and Drug Administration) is responsible for setting and implementing regulations for the registration, manufacturing, distribution, and monitoring of medical devices and pharmaceuticals in China.	Adverse event reporting or vigilance reporting: Manufacturers and users have the duty (it is compulsory) to report all adverse events that could have potentially led to patient harm within 5 days of their occurrence (Tarricone *et al*.) (31).	Medical Device Adverse Event Monitoring System (See Appendix 3: Medical Devices Regulations, HTA bodies and other institutions worldwide with a mandate over medical devices (Table 4)).
Japan	The Pharmaceutical and Medical Device Act (PMD Act)(43). The PMD Act is the key regulatory framework overseen by Japan's MoH, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA). The PMDA operates under the MoH, Labour and Welfare (MHLW) and is tasked with evaluating and approving pharmaceuticals and medical devices to ensure their safety and efficacy.	Adverse event reporting or vigilance reporting: Reporting of adverse events by outlining the responsibility of both medical device manufacturers and healthcare practitioners to promptly report such events and take corrective measures. (Act 60.10 of Ministerial Ordinance No. 169 Japan)	"J-MDNR" (Japan Medical Device Nomenclature for Registration) system.
Brazil	RDC (Resolution of the Collegiate Board) 185/2001(44). Brazil's legislation for medical devices is aligned with the GHTF. National Health Surveillance Agency under the MoH (ANVISA) is responsible for the registration of medical devices, National Health Surveillance Agency under the MoH (ANVISA) is responsible for the registration of medical devices, it centralizes pre- and post-market surveillance phases. There are two regulatory pathways for market approval of medical devices: notification, a simplified process for devices that are considered lower risk and registration for high-risk devices listed in the ANVISA normative instruction IN 2/2011(45).	Adverse event reporting or vigilance reporting: As well as in Australia, reporting by stakeholders other than manufacturers is encouraged, but mandatory for sponsors/manufacturers.	Online system provided by the Agência Nacional de Vigilância Sanitária (ANVISA), the National Health Surveillance Agency

Tarricone *et al.* (2014) described:

> ***Classification of MDs in jurisdictions**: "basis of medical device classification at the national level is: the risk associated with the device; manufacturers' intended purpose for the device and the device's indication for use. (...) the device class determines (...) the level of evidence and evaluation required to demonstrate safety and efficacy",* so that, Medical Devices are *"categorized into three or four classes, with class III (USA, Europe, Australia and China) or III and IV (Canada, Japan and Brazil) representing the highest risk category.*
>
> ***Evidence requirements for premarket approval:***

- *EU:*

  Conformity assessment under a Notified Body (NB).

  Methodological evaluation based on scientific evidence for safety, performance, design, and intended purpose.

- *USA:*

  PMA process by FDA.

  Requires preclinical and clinical studies.

  Controlled Trial (not necessarily randomized) or clinical studies for HRMDs with a flexible design under 510(k).

- *Canada:*

  Health Canada oversees ISO quality system.

  Requires preclinical and clinical studies, including RCTs for class III and IV devices.

- *Australia:*

  TGA mandates clinical evidence, including data from trials, post-market surveillance, and literature.

  Focus on performance and safety evaluation for the intended use.

- *Japan:*

  PMDA follows GHTF and ISO as "Gold standards".

  Requires laboratory testing and clinical trial consultation for efficacy and safety evidence.

- *Brazil:*

  INMETRO and ANVISA demand "product-specific resolutions" and an Economic information report.

Clinical trial evidence required, especially for high-risk and novel devices.

- *China:*

  Two types of clinical trials for HRMDs: clinical testing for new products and clinical verification for comparing products in the market.

  Verification ensures equivalence in structure, performance, safety, and effectiveness.

  Requirements for post-marketing surveillance & vigilance: In all seven jurisdictions, the licensing or registration process also imposes obligations on the manufacturer for post-market surveillance. This phase remains different among the different countries despite the objective of GHTF. In China not only for manufacturers but users it is compulsory to report Adverse events related to injury or death. In the USA it is a duty for manufacturer, distributor, competitor, healthcare providers and patients. In the EU it is optional for practitioners and medical institutions, while in Brazil and Australia it is compulsory for manufacturers. In addition, the deadline to report these adverse events is crucial "*In the USA (...) the adverse event within 30 days following the date of awareness and within 10 days if the event caused death or serious deterioration in the state of health, and in Australia within 48 h if the event represents a serious threat to public health"*, This information is publicly available in real time. In the EU, manufacturers notify these events which are published in real time, while improvements and corrections are published as Field Safety notices. However, there is no limit or specific timeframe for this process. There is no mention about the surveillance and vigilance points referred to adverse events notifications and time to submit this information.

Rey-Ares *et al.* (2016) described:

Regulatory Requirements for High-Risk Devices:

Argentina: Unspecified evidence clinical trials required for class III and IV devices.

Brazil: ANVISA mandates a technical report for class III and IV, based on clinical trials, with a maximum license duration of 10 years.

Colombia: INVIMA demands a comprehensive report for class IIb and III devices, including safety, efficacy, technical details, quality of manufacture, and supporting clinical trials or equivalent technologies.

Mexico: COFEPRIS allows equivalence review for devices registered in the USA, Canada, or Japan, known as the sanitary registry, taking 4 to 12 months. Class III device licenses granted based on clinical trial evidence with no specified minimum strength required.

***Post-licensing Surveillance*:** all the countries perform actions related to adverse events and notifications taking different actions from cancellation to recall. But there is no specification about how these mechanisms are developed.

Reckers-Droog *et al.* (2020) described:

Research design is complex due to the multifactorial nature involved in medical devices. In fact, to perform a CED scheme there must be a guideline or protocol to reduce the variability and the uncertainty. However, when requirements and laws are not quite defined with respect to medical devices, registries where data is stored to perform safety and vigilance studies don't have a standard classification of this information, which makes it difficult to determine if a Controlled trial or an observational study should be performed in many cases. This problem is even more difficult when the funding comes from profit institutions involved in production and manufacture of health products. Out of 4293 records, 70 were retrieved, yielding 27 eligible articles. Six articles discussed challenges in CED schemes for specific medical devices, while 21 covered various types. Authors identified 17 challenges, including deciding on scheme desirability, understanding risks, complex negotiations, defining decision problems, data requirements, meaningful outcomes, scheme duration, new technology entry, funding, informed consent, data quality, success criteria, technology withdrawal, transparency, governance, stakeholder involvement, and ethical issues. For details, refer to **Table 2 - Post-market reporting activities: Main outcomes** and **Table 4 - Appendix 3: Mapping of regulatory frameworks, regulatory bodies, and HTA bodies worldwide and their role in the access pathway for medical devices**.

Pane *et al.* (2021) described:

Post-market Surveillance Databases: These databases play a crucial role in monitoring the performance and safety of medical devices after they enter themarket. They include well-known repositories such as the FDA MAUDE database in the US, TGA DAEN database in Australia, and the anticipated EUDAMED in the EU.

Adverse Event Triggered Reporting for Devices: (ASTER-D) (US), MEdical DEvices VIgilance and Patient Safety (MEDEVIPAS) (Greece), and the National Electronic Injury Surveillance System (NEISS) (US).

10 registries were identified for post-market surveillance: American College of Cardiology's National Cardiovascular Registry (US), Massachusetts Angioplasty Registry (US), Kaiser Permanente Orthopedic Implant registries (US), National Cardiovascular Data Registry (NCDR) (US), database of Sprint Fidelis and Quattro Secure implantable cardioverter defibrillator leads (US), Swedish Coronary Angiography and Angioplasty Registry (SCAAR) (Sweden), European Registry of Quality Outcomes for Cataract and Refractive Surgery (EUREQUO) (EU), Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) (Australia), Data Extraction and Longitudinal Trend Analysis (DELTA) Registry (US), and Medicare database (US).

Another issue dealt in this review were Signal Detection Methodologies: *Spontaneous Reporting System, signal detection methodologies applied to registries and optimal signal detection methodologies for medical devices without applying the methodology to a specific type of PMS data source* were the main points. However, signal detection methodologies applied to non-standard data sources were not considered. *"Of the four articles that included signal detection*

methodologies applied to registries, all four articles discussed methodologies associated with the Data Extraction and Longitudinal Trend Analysis (DELTA) network".

The following Coding Dictionaries were identified: ISO (FDA codes and International Organization for Standardization), IMDRF (product adverse events and research results), SNOMED-CT (Systematized Nomenclature of Medicine- Clinical Terms), MedDRA_, ICD (International Classification of Diseases), FDA Patient Problem and IMDRF (Patient Codes for patient outcomes).

Krüger & Wild (2013) described:

-USA- FDA 510(k) process explicitly allows market entry to some HRMDs under evidence requirements from manufacturers. This evidence implicate a report of similar results with similar technologies which contains a technical section subdivided into the non-clinical laboratory studies section ("*information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and any further laboratory or animal tests*") and the clinical investigation section (*"information on the study protocols, safety and effectiveness data, adverse reactions and complications, device failure and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations is required"*). The time period to determine the market viability or denial of class III HRMDs is 180 days.

-EU- information was focused according to the previous legislation: AIMD (90/385/EEC, 20th of June 1990), MDD (93/42/EEC, 1st of January, 1995), and IVDD (98/79/EC). With regard to the market circulation, the process that all medical devices must undergo is carried out by NBs, which decide if the conformity assessment is provided to a product in case safety and efficacy data have been provided by manufacturers. Nevertheless, in case of class IIb, class III and implantable medical devices "*Clinical investigation must be performed to confirm or refute the manufacturer's claims for the device*". This type of evidence must contain essential requirements: "*data concerning the chemical, physical, and biological properties, infection and microbial contamination, construction and environmental properties, labeling and information leaflet for users*". In addition, NBs may require this information to be published as clinical investigations or others called equivalence-data.

-Australia- the TGA must receive a uniform national standard through the *Australian Register of Therapeutic Goods* (ARTG), which in other medical devices apart from class I, should inform about quality, safety, and performance requirements. Within this conformity assessment report information requested must contain "*general details of the device, the application scope, whether it is a new device, a device like one that already exists, or a recertification, the manufacturer's details, including facility, and whether the device has already been marketed in other countries and received certification. Further, a critical supplier's form has to be filled in. (...) The general principles include evidence about the intended use, the safety principles, especially long-term*

safety, the transport and storage, as well as the risk ratio. The design and construction principles contain evidence about chemical, physical and biological properties, infection and microbial contamination, construction and environmental properties, measuring function or radiation, information supplied by the manufacturer and all relevant clinical evidence".

-Canada- *The Medical Devices Bureau of the Therapeutic Products Directorate* (TPD) within *Health Canada* expend a license to those manufacturers that had accredited a Notice of Compliance (NOC), and with respect to class II, class III, and class IV medical devices, it is compulsory a Medical Device License, obtained through Medical Device License submission. Requests from this submission vary from safety and effectiveness evidence (Class II) and additional labeling and packaging (Class III) to quality and risk management assessment in a review form in a timeframe of 75 to 90 days. In case of Class III devices, manufacturers must collect a summary of results from studies performed about safety and effectiveness, labeling, packing and production data in order to obtain the market approval. On the other hand, Class IV medical devices have to submit risk assessment data, the quality plan and the manufacturing process plus evidence requirements from Class I-III.

In addition, despite the USA, Australia and Canada being quite explicit with regard to the quality of evidence for submission plans, promoting the RCT´s as gold standard's quality evidence, the EU NBs are granting the CE marking with little clinical quality studies. This decentralized system which allow manufacturers freely choose the Assessment competent authority for assessment of their medical devices, is highly differentiated and criticized in comparison to the approval for PMA or 510(k) clearance (USA), the ARTG number (Australia), or the Device License (Canada), which in addition are publicly available.

Carbonneil *et al.* (2009) described:

The Access with Evidence Generation (AEG), also referred to as CED (hereafter in this report we will refer to this type of schemes as CED) is relevant during technology's life cycle for marketing approval as well as for coverage.

There is much less information about medical devices than from medicines/drugs postmarket safety/vigilance.

With regard to Medical Devices, from twenty-three countries revised just seven (Australia, Canada, Latvia, Spain, Switzerland, United States and UK) identified AEG tools for marketing approval:

- **Conditional Licensing:** this mechanism from Canada is established for HRMDs whose safety and effectiveness are granted but it is necessary to complement with clinical evidence and verify the benefit/risk ratio in a timeframe deadline.
- **Postmarketing Clinical Follow-up** (or Postapproval Surveillance): FDA (USA), Health Canada (Canada) and Department of Health and Human Services (HHS), FDA, Center for Devices and

Radiological Health are described as available tools for long-term surveillance of patients included in clinical studies from pre-approval stages.

- **AEG Mechanisms Associated with Coverage Decisions:** At the date of the study twelve countries (Canada, Spain, Australia, United States, Switzerland, Sweden, Belgium, Netherlands, France, England/Wales, Germany and Italy had implemented AEG before coverage decisions. These mechanisms are classified according to the level of incertitude: <<*No, unless*>> (not enough evidence for coverage)*; <<Yes, but*>> (there is enough evidence to allow coverage in the event evidence is continued being generated)*; and <<Yes for now*>> (evidence is enough to allow coverage). From already mentioned countries, all of them except Germany and Italy implemented a "*conditional coverage*" as AEG mechanism, with the requirement to generate evidence for decision makers. This postulation corresponds to <<*yes, but*>> level, and it is re-called depending on the country in which is established: Conditionally funded field evaluation (Canada); Monitored use (Spain); Interim funding (Australia); CED (United States); Medical Service under evaluation (Switzerland); Reimbursement with conditions (Sweden); Conditional reimbursement (Belgium & Netherlands); and Still in clinical research (France). Data requested for evidence required is extracted from clinical trials and registries or prospective and health economics studies under real-life conditions. See *Table 3. Reported Strengths and Weaknesses of AEG Systems at the Coverage Stage;* and *Table 4. Degree of Implementation of AEG Mechanisms by Various Countries* from Carbonneil *et al.* (2009) (36).

Baeyens *et al.* (2015) described:

The report covers the EU and US systems concerning the regulation of Medical Devices, discussing topics such as device classification, pre-market evaluation, time to market, reimbursement, and examples of system failures. It delves into the EU's regulatory framework, emphasizing the free movement of goods, medical devices directives, patients' rights in cross-border healthcare, and proposing new regulations. The report also explores national-level measures, including restrictions on distribution, medical guidelines, registries, and healthcare professionals' behavior rules. Finally, it suggests possible solutions for Belgium, covering measures within and outside harmonized fields, increased healthcare professional obligations, and the use of registries and post-marketing surveillance.

No information about the design of studies selected, the number of studies according to the selection criteria, or a flow chart with characteristics from the information selected studies is given in this report.

T*he Medical Device Safety Action Plan:* *Protecting Patients, Promoting Public Health* from the FDA provides how << "*to assure the safety of medical devices throughout the TPLC (Total Product Life Cycle), to provide for the timely communication and resolution of new or increased known safety issues, and to advance innovative technologies that are safer, more effective and address unmet needs*>>.

Concerning the topics in this document, they are structured as follows:

- **Framework for device oversight:** Three risk-based classifications (1.- Class I devices; 2.- Class II devices - *"510 (k) submissions that provide a demonstration of substantial equivalence to a legally marketed predicate device"*; 3.- Class III devices - *"premarket applications (PMAs) containing clinical and non-clinical data to determine whether there is a reasonable assurance of safety and effectiveness for these devices"*).

  Methods and Techniques used under FDA's authority to assure effectiveness and safety (1.- Medical Device Reports (MDRs); 2.- Medical Product Safety Networks (MedSun); 3.- Post-approval studies; 4.- Postmarket surveillance studies (also referred to as "522 studies"); 4.- Premarket approval application annual reports; 5.- Review of the scientific literature; 6.- Inspection of device establishments for compliance with quality system and other applicable requirements; 7.- Manufacturer reports of corrections and removals, 8.- Complaints and allegations made by members of the public, often by competitor companies).

- **Modern enhancements to FDA oversight of device safety:** 1)Establishing the UDI system; 2) Improving regulatory clarity regarding use of Real World Evidence ("*leveraging real world data sources has helped address the current challenges with patient enrollment in post-approval and other postmarket studies (...) FDA's use of real-world evidence to support regulatory decision-making for medical devices holds tremendous promise to incentivize development of robust new sources of evidence of device safety and effectiveness, in less time and at lower cost than ever before*"); 3) Developing the National Evaluation System for Health Technology (NEST) a "*surveillance and evaluation system that complements the passive surveillance approaches currently in use*"; 4) The CDRH Signal Management Program; 5) Recalibrating the benefit-risk framework for device oversight in the pre- and postmarket settings; 6) Creating a competitive marketplace for device quality; 7) Addressing the cybersecurity of medical devices as a patient safety concern.
- ***Action Plan*:**

  1- *Establish a robust medical device patient safety net in the United States* in agreement to the initial NEST initiative.

  2- *Explore regulatory options to streamline and modernize timely implementation of postmarket mitigations* trying to impose special controls for sudden high-risk events derived from medical devices.

  3- *Spur innovation towards safer medical devices*, like "*Establish a voluntary, more modern 510(k) pathway for demonstration of safety and effectiveness for certain moderate risk devices*".

  4- *Advance medical device cybersecurity*. For that purpose, among different actions, FDA may: "*Consider new postmarket authority to require that firms adopt policies and procedures for coordinated disclosure of vulnerabilities as they are identified*".

5- *Integrate the CDRH's premarket and postmarket offices and activities to advance the use of a TPLC approach to device safety*.

4.2 Results from Survey of Notified Bodies experiences

Before the introduction of the EU MDR, in 2017, approximately 78 certified NBs were authorised to conduct conformity assessments under the MDD or AIMDD (46). However, the implementation of the MDR mandated that all designated NBs undergo a comprehensive re-evaluation. In consequence, there has been a significant decline in the number of approved NBs, and subsequently in their collective capacity. According to the NANDO website (September 2023), the latest data indicates that there are now 40 fully approved NBs under the EU MDR.

The survey was distributed in March 2023 to 61 members of 40 NBs. There were, at the time when this survey was distributed, 50 NBs designated under Directive 93/42/ECC, 38 under the new MDR (EU) 2017/745 and 30 under both the MDD and the new MDR (numbers extracted from the NANDO website[1] – see webpage for further information).

Responses from 13 NBs were received (Table 1). Out of 40 NBs that were invited to participate in the survey, 23 did not respond and they did not explain why they could not or did not provide us with the requested information. Four NB representatives, as a reason for not being able to participate in the survey, declared that: 1) they were being asked to participate in too many surveys and did not have capacity to provide the requested information, and; 2) due to their lack of experience with the topic at hand, they could not participate, and forwarded the message on to the responsible person within their organisation (however, no response was registered afterwards either).

According to data collected in the survey, 2602 certificates in total were granted for Class III and implantable medical devices under the MDD and AIMDD, ranging from o to 1000. This data was obtained from 11 NBs participating in the analysis. Notably, one of the NBs provided an approximate count of ≈ 1000 certificates issued within their jurisdiction. Two NBs did not provide data regarding either the total number of issued certificates or certificates that were rejected. These NBs stated that no certificates were issued with any restrictions or limitations during the period under examination. 327 certificates were rejected, which comprised 11% (0-20) of the total number of issued certificates (data from NBs that did not provide information about the total number of issued certificates have not been included in this calculation; N=2). Three NBs issued certificates with restrictions or limitations corresponding to 1% of the total of certificates issued (0-2.5; N=2). However, it is not possible to calculate the rate of certificates issued with restrictions or limitations for one of those NBs (See the Table 3). Of those NBs, two provided additional data (4 and 3 issued certificates/NB) on the characteristics of the medical device and the nature of the imposed restrictions or limitations. Specifically, the following types of HRMD were granted with these certificates: adhesion barrier, implantable suture, dermal filler, surgical mesh, implantable glucose sensor, leadless pacemaker and implantable brachytherapy seed for treatment of pancreatic cancer. With

[1] The NANDO website is: https://webgate.ec.europa.eu/single-market-compliance-space/#/notified-bodies

regard to the nature of the restrictions or limitations, four of the certificates were issued with a restriction on their intended purpose and three restrictions were associated to the novelty of the medical device indicated in the regulatory application, and to concerns related to the safety and performance of the device, with instructions to undertake a PMCF study (for details see **Table 3 - Results of the Survey of Notified Bodies experiences: Medical Device Regulation of high-risk devices**).

Table 3. Results of the Survey of Notified Bodies experiences: Medical Device Regulation of high-risk devices

NB	The total number of certificates issued for Class III and implantable medical devices under the MDD and AIMDD*	Number of applications for certificates of class III and implantable MDs that were rejected within the scope of the MDD and AIMDD*	Number of certificates issued for class III and implantable MDs with restrictions and limitations in accordance with the MDD and AIMDD*	Intended purpose, indications, area of medicine, and the type of restriction or limitation that was placed on the certificate		
				Medical Device	Intended purpose, indication and area of medicine	Nature of the restriction or limitation
1	305	35	0			
2	50	2	0			
3	1000*	200	25			
4	14	0	0			
5	47	0	0			
6	impossible to estimate	impossible to estimate	0			
7	34	2	0			
8	0	0	0			
9	30	8	0			
10	118	5	0			
11	441	75	4	Adhesion barrier	To protect adhesion after the surgical procedure	Restriction of intended purpose
				Implantable suture	Wound healing	Restriction of intended purpose
				Dermal filler	Soft tissue augmentation	Restriction of intended purpose
				Surgical mesh	To provide additional support when repairing weakened or damaged tissue	Restriction of intended purpose
12	563	0	0			

13	impossible to estimate	impossible to estimate	3	Implantable Glucose Sensor	Endocrinology	Novel technology. Concerns raised by both notified body and competent authority during medicinal assessment around the unknown risks associated with repeated 6 monthly administration of a steroid during the implant. Concerns raised around the long-term performance of the sensor if fibrosis of tissue was to occur. Condition of certificate required every implant to be enrolled into a registry and a PMCF study to be performed. **Additional comment:** Certification continued without any concerns identified through PMCF activities. Manufacturer was required to report safety and performance to the notified body every three months alongside reporting vigilance episodes with the required legal timeframes
				Leadless Pacemaker	Cardiology	Novel technology. First to market. Clinical data demonstrated good safety and performance in a cohort of patients not eligible for conventional pacemaker, however lack of longer-term data that reflect the expected lifetime of the device (10 years). Condition of certificate required every implant to be enrolled into a registry and a PMCF study to be performed **Additional comment:** Certificate cancelled after 2 years following a report submitted to the notified body of increased vigilance episodes. Manufacturer was required to report safety and performance to the notified body every three months alongside reporting vigilance episodes with the required legal timeframes.
				Implantable brachytherapy Seed for treatment of Pancreatic Cancer	Oncology	Novel technology. First to market. Clinical data demonstrated good safety and performance in a cohort of patients not eligible for resection (terminal diagnosis). This was considered an unmet medical need that the initiation of this treatment did not impact current standard of care. Little development with chemotherapy agents for many years in the treatment of pancreatic cancer with little successful outcomes. Condition of certificate required every implant to be enrolled into a registry and a PMCF study to be performed **Additional comment:** Condition of certificate remains in place. Manufacturer is required to report safety and performance to the notified body every three months alongside reporting vigilance episodes with the required legal timeframes.

*Time horizon: 01/08/2012 – 26/05/2021

** Approximation, no exact data can be obtained

5. Discussion

The aim of this report was to analyze the kinds of provisions in place in the European regulation for HRMD for post-marketing evidence generation. In the EU, the regulation of medical devices in EU involves a combination of responsibilities among various entities. NBs assess the conformity of the evidence supporting the use of specific medical devices with the regulatory requirements described in the European regulation for medical devices. To grant access to the European market, they are responsible for ensuring their safety and efficacy. The CE marking is the administrative process used by the European Commission to issue marketing authorizations for medical devices. Our research focuses on how NBs set restrictions and limitations imposed by NBs on "*Certificates of conformity*" given for HRMD on the EU market (2). As a secondary research aim, we extract lessons on how post-marketing evidence generation is organized in the regulation for medical devices in jurisdictions outside of the EU and/or from the regulation of medicines (within or outside the EU), to extract potential learning applicable to the regulation of medical devices in Europe.

Post-marketing evidence generation can be useful to answer questions posed by regulators when, at the time of regulatory assessment, there are uncertainties that need further evidence to be addressed. But they can also be useful to generate evidence of comparative performance, relevant for HTA bodies, when such evidence is weak at the time when the technology reaches HTA bodies (10). Therefore, to add to the evidence derived from our survey and review, we decided to supplement it with a mapping of the regulatory bodies, HTA institutions and Ministries of Health (MoH) with a role in the access pathway for medical devices in their jurisdictions (See Appendix 3 - Medical Devices Regulations, HTA bodies and other institutions worldwide with a mandate over medical devices) in order to offer additional information about the regulatory and legislative fields for HRMD in this report. This appendix attempts to anchor our results in the purpose of the CORE-MD project and the entry into force of the Medical Device Regulation (EU) 745/2017 (MDR), attempting to provide evidence that could help improve the safety and surveillance phases of the life cycle of a HRMD. By signposting how restrictions and limitations are taken into account for the continuity of the CE marking of an HRMD in accordance with the "certificate of conformity" issued by the NBs (47–49), we intend to offer evidence that is useful for policy makers in future developments.

We divide our findings in the following topics to provide them in a structured manner, segmented in the different areas related to regulation of HRMD.

5.1 Premarket entry for Medical Devices

Some institutions grant marketing authorisations for types of health products conditional on generating postmarket evidence as a requirement to guarantee the safety and effectiveness of these products, usually in the case of HRMD (35,38,50).

As it happens with medicines, for some medical devices a regulatory requirement is the submission of a report which must be assessed by their corresponding regulatory authority depending on the country or international jurisdiction, as the FDA in the case of the USA (Premarket approval -*PMA*; and *510(k) pathway*), or a NB in the case of the EU (9,24).

- In the USA, the FDA has the *510 (K) pathway*, which implies a time period of 180 days to determine the market viability for class III HRMD (51,52);
- in the EU the *Clinical Evaluation Assessment Report* (*CEAR*) plays a similar role, and the timeframe for being submitted varies from 9 to 18 months (53);
- in Australia, the TGA referred this process as an *Application Audit Assessment*, whose timeframe for submission is from 8 to 12 months, and it consists on a previous submission of a *Uniform National Standard* (6 months) and, after its approval, it is compulsory to submit a *Conformity Assessment Report* (which varies from 2 to 6 months) for HRMD (41);
- in Canada, the TPD from Health Canada requires for a Medical Device License to be subject to deliver a review form in a timeframe of 75-90 days collecting a summary of evidence generated about safety and effectiveness.

Nevertheless, on top of these pre-marketing requirements, the duty of regulators is also concerned with post-marketing evidence generation. This phase of a TPLC is the focus of this report. Especially when the variability given among different countries in the requirement submission data for HRMD reporting is a crucial point for manufacturers to introduce a health product in the market of a determined country (37).

5.2 Overview

From 7 selected articles, all of them were critically low- or low-quality reviews. No articles discussed conditions or restrictions on certificates imposed on HRMD by regulatory bodies, which was the primary objective of our review. 2 articles discussed coverage CED restrictions imposed on HRMD by national health technology assessment authorities. In addition, the countries included for data extraction were heterogeneously selected: five reviews focused on USA, Australia, Canada and the EU (this one with different countries selection, further details ahead on the text) (33–36,50). Three reviewed Brazil (32,34,50), 2 reviews took into account Japan (34,50), and Argentina Colombia, and Mexico were just once mentioned by Rey-Ares *et al*. (2016) (32). Baeyens *et al*. (2015) did not provide information about it(37). With regard to the countries from the EU, only 3 documents analysed the situation in the following countries: The Netherlands and Germany (33,35,36); France, Belgium, Spain and England (33,36); Austria (35); and Finland, Denmark, Italy, Latvia and Portugal (36).

Nevertheless, one of our findings is the misstructured standardization of the data from the different jurisdictions. To facilitate the mapping of differing practices around the globe, we have produced a table (in Appendix 3: Medical Devices Regulations, HTA bodies and other institutions worldwide with a mandate over medical devices (Table 4)) where to find the actual information from different countries and their

regulatory and HTA state of the art (e.g.: in the USA, the current law in medical devices regulation is *the Title 21 of the Code of Federal Regulations*, from March 2018).

5.3 Medical Devices Classification

With regard to the classification of Medical Devices worldwide, medical devices are categorized in different groups based on the level of risk involved in using them in different countries, emphasizing that the highest risk ones may differ among countries belonging to class III and/or IV (32,35,38,50). However, data retrieved makes us concerns about why there are some countries or jurisdictions with variations in the classification of health technologies as medical devices. Due to this lack of framework, this report describes in Appendix 3 (Medical Devices Regulations, HTA bodies and other institutions worldwide with a mandate over medical devices) the different risk classification systems for medical devices according to regulation and laws in force nowadays in each of them, including additional information about the approach used in HTA for the classification of devices (extracted from the three main HTA' networks in the world (54).

For instance, in the United States, the US FDA is the national regulatory body. The FDA recognizes three classes of medical devices according to the risk derived from their use in human health. In case of HRMD (Class III), manufacturers must carry out a protocol (see the next section for more details) to obtain a marketing authorization for their product, and one of the conditions to allow the entry of this product is the surveillance and the evidence generation derived from its use in the current clinical practice of the U.S. through the *Medical Device Safety* database.

5.4 Post-marketing evidence generation: lessons for High-Risk Medical Devices

In this section, we include all activities intended to report or collect safety or efficacy data for HRMDs with a CE mark (or a marketing authorization if we describe cases outside of Europe).

In China, the CFDA makes it compulsory for manufacturers and users to report injury or death derived from the use of a HRMD. In the USA, the reporting act is a duty for manufacturers, distributors, competitors, health providers and even for patients. With regard to Brazil and Australia, these impose this task as an obligation mainly for manufacturers. On the other hand, in the EU adverse events and device deficiencies that occur during clinical investigations should be reported to the Member States in which those clinical investigations are being conducted and submit the reports to EUDAMED database (50).

The licensing timeframe to market with a HRMD is an important factor, relevant for post-marketing evidence generation. Rey-Ares *et al*. (2016) describe how heterogeneity of licensing timeframes around

the world, as well as the evidence requirements imposed on marketing authorization holders relative to the submission of evidence supporting the continued use of their product, set the frame for post-marketing evidence generation activities in different regions (32). We found no justification for the heterogeneity reported in the literature around the differences in time to market (licensing timeframes) for medical devices.

The Event Reporting Databases are relevant for post-market surveillance, since it is there where data related to injury or death from the use of HRMD is going to be stored (55–57). Nevertheless, these types of health data storage have evolved according to some guidelines from corresponding authorities, for example, giving place to EUDAMED in the EU (47,49,58). This database, according to the new MDR(2,19), will provide "*a living picture of the lifecycle of medical devices*" into the European market, whose main purpose is to enhance transparency and make information public, improving as a result the availability of information for the different stakeholders (patients, healthcare providers, politicians, etc.), that will be structured in the following sections: actor registration, unique device identification (UDI) and device registration, NBs and certificates, clinical investigations and performance studies, vigilance and market surveillance.

In addition, the nature of these data has allowed the Signal Detection Methodologies emergence to evolve in the retrieval of Real-World Data (RWD) allowing Real-World Evidence (RWE) and their application in evidence generation as Data Extraction and DELTA' studies (13,59–62). The fields of RWD and RWE generation for HRMD, include innovative study designs that could be taken into consideration, although there is still scarce evidence of their use in this field up to now (56,63–66). An example comes from the United States, where the *Medical Device Safety Action Plan* from the *U.S Food & Drug Administration justify* is using DELTA studies as an attempt to apply RWE as a Surveillance tool (38). Overall, as Reckers-Droog *et al.* described (33) and Baeyens *et al*. (2015) presented (37), an existing gap in this field is that there is neither a standard of data classification to store safety and vigilance studies, nor a guideline standard to execute this task.

The shift in the EU's regulatory landscape for medical devices, brought about by the introduction of the MDR and IVDR represents a significant step forward in ensuring the safety and effectiveness of medical devices within the EU. The results of the survey shed light on the practical application and how the system functioned before the MDR was implemented in full. The MDR, which came into effect in May 2021, introduced more stringent requirements for medical device manufacturers, leading to a surge in the workload of NBs responsible for assessing compliance with these regulations. This has created challenges in terms of timely recertification and assessments of medical devices, impacting both manufacturers and the NBs themselves (67).

First of all, worth to be highlighted the significant challenges faced by NBs in the medical device industry due to an overload of work and a lack of capacity. NBs emphasise current limitations in serving clients and the reduction in capacity due to the increased workload caused by recent regulatory changes, ongoing maintenance of MDD certificates, a steep learning curve, a decrease in the number of operating NBs,

difficulties in finding skilled workers, and a lengthy process to become a notified body (68). Already in 2022, the Medical Devices Coordination Group (MDCG) in the position paper discussed suggestions on how to address the problem of the NBs capacity, access to NBs and manufacturers' preparedness in order to facilitate transition to the MDR and IVDR and to avoid shortage of medical devices (18). Similar opinions were expressed during our group consultations with NBs representatives as well as a justification to several rejections to participate in the survey. That could also explain the substantial difference between NBs in terms of the quality of their responses and their ability to justify their decisions - only 2 NBs have provided details of the medical device granted with the conditional certificate and details of that conditional approval.

Through extensive discussions with NBs working alongside CORE-MD, regulatory authorities, participants in the CORE-MD consortium and finally form our survey (despite very limited number of responses) it became evident that the utilization of 'conditions' has been notably constricted.

This situation has presented significant difficulties in conducting a forward-looking examination of the regulatory effectiveness of 'conditions' under the MDD. This challenge is further compounded by the fact that NBs were already overwhelmingly occupied with the re-evaluation of existing medical devices for compliance with the MDR. Recently released by the European Commission the proposal to extend deadlines to comply with the MDR and IVDR (*Regulation Of The European Parliament And Of* The Council amending Regulations (EU) 2017/745 and (EU) 2017/746 as regards the transitional provisions for certain medical devices and in vitro diagnostic medical devices) highlights the fact that due to the limited authorization of NBs under the new regulations, there is insufficient capacity to promptly issue certifications of conformity for all devices in need of certification or re-certification by the end of the transition period and that could be threatening the availability of medical devices on the EU market. On the other hand, many manufacturers are not adequately prepared to meet the more stringent requirements imposed by these regulations. Finally, the EC also attributes the exacerbation of the situation to the impact of the COVID-19 pandemic and the war in Ukraine that has also influence on the availability of medical devices in the EU market, increasing the risk of shortages that could impact the healthcare needs of European patients (*Regulation Of The European Parliament And Of* The Council amending Regulations (EU) 2017/745 and (EU) 2017/746 as regards the transitional provisions for certain medical devices and in vitro diagnostic medical devices).

The responses from a subset of NBs reveal that only a limited number of certificates were issued with restrictions or limitations, representing a small fraction of the total issued certificates. This data provides valuable insights into the real-world implementation of the "conditional" certification approach. Out of 7 certificates with restrictions or limitations, 4 were issued with the restriction of intended purpose that involves clear defining the scope of the device's intended use, outlining the conditions under which it has been demonstrated to meet safety and efficacy standards (MDR Article 56). The goal is to establish the boundaries within which the device can be safely and effectively employed, preventing any misuse or off-label use that could pose risks to patients.

It is worth mentioning that in case of three certificates issued for implantable glucose sensor, leadless pacemaker and implantable brachytherapy seed the condition of certificate required every implant to be enrolled into a registry and a PMCF study to be performed that ensures a meticulous tracking of each device in real-world performance and emphasizes the need for ongoing scrutiny of these novel devices. Continuous monitoring through registry enrollment and PMCF studies enables the collection of valuable data on long-term safety, efficacy, and potential device-related complications. In the position paper (Team NB Position in Response to MDCG 2022-14 Item Number 17 – 'Certificates under Conditions') TEAM-NB has addressed the issuing certificates under conditions stating that the issuance of certificates with conditions without comprehensive conformity assessments poses a risk of certifying devices lacking sufficient clinical or technical evidence, compromising patient safety and contradicting MDR principles. Particularly for high-risk devices relaxing requirements on clinical evidence during certification goes against the expectations of EU Expert Panels. Furthermore, imposing conditions on certificates demands heightened post-market surveillance by NBs, increasing scrutiny and follow-up activities. Issuing certificates with conditions regularly puts a strain on NBs, reducing their capacity and potentially compromising the effective oversight of medical devices in the market due to the increased burden of enhanced surveillance. Results of our survey go in line with the approach of TEAM-NB regarding certificates with restrictions or limitations.

6. Summary and conclusions

The main finding of our research is that the evidence published around the application of conditions on certificates of conformity of medical devices in Europe is extremely limited. Our survey allowed us to generate novel evidence, and our review of the literature summarized the limited evidence that was already out there, and allowed us to identify examples from other competent authorities that apply schemes similar to restrictions to certificates of conformity, and that could orientate potential future reforms in Europe.

Our key findings and discussion points are:

- The possibility for NBs to impose limitations on certificates of conformity is contemplated in the new European regulation for medical devices, but this pathway is not sufficiently developed, which has led to this option barely being used in practice, as shown in our survey results.
- The sporadic utilization of certificates with conditions may indicate a careful stance adopted by NBs, placing a strong emphasis on rigorous examination and strict adherence to regulatory standards at the time when the certificate is first issued. This approach could lead to a reduced number of cases where NBs make use of the route to provide access to HRMD that respond to an unmet medical need but provide less comprehensive clinical data than normally required, where the benefit of immediate availability of the device outweighs the risk inherent in the fact that additional data are still required.
- Several HTA authorities have established Coverage with Evidence Development (CED) schemes for HRMD, but without a sufficiently developed regulatory predecessor in Europe, there is no regulatory route for the kinds of HRMD that would be likely to benefit from these kinds of schemes.

Recommendations:

- Medical devices should be classified in a commonly standardized classification system worldwide.
- There must be an active effort to regularize the way by how to supervise the HRMD surveillance by the stakeholders and, in the case of EU, the CE marking evaluation.
- It is necessary to improve the event reporting tasks in order to reduce the variability and heterogeneity of HRMD data derived use reflected in the existence of multiple registries and databases all around the world.
- There are examples from other competent authorities that could serve the EU as inspiration, such as the US FDA Breakthrough program for medical devices (69) and the NMPA's (the competent Chinese Regulatory Authority) Guideline on Conditional Approval for Medical Devices for instance (70).
- Further research on legislation and regulation is required to ensure public health and reduce injuries or deaths derived from the use (or lack of access to, and subsequent use) of HRMD. Further development of policies supporting the application of limitations to certificates of conformity, further defining the situations that would be appropriate for the application of such

regulatory instrument, could enhance access to HRMD with promising evidence whilst enabling the development of further evidence.

- The survey responses, including a lack of participation, may suggest a potential lack of acceptance within the NBs regarding the practical application and benefits of certificates with conditions.

Limitations

Despite our documents are not explicitly clinical in order to perform the quality assessment with AMSTAR-2 checklist, we employed this tool due to the lack of a specialized tool to evaluate the evidence quality of regulatory documents in research.

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Appendices

Appendix 1: Prospero's CRD 42023431233

Post-approval evidence development schemes established by regulatory authorities for high-risk medical devices. A protocol for a systematic review.

To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided here.

Citation

Jesús Aranda López, Agnieszka Dobrzynska, Maria Piedad Rosario Lozano, Juan Carlos Rejón Parrilla, David Mark Epstein, Juan Antonio Blasco Amaro. Post-approval evidence development schemes established by regulatory authorities for high-risk medical devices. A protocol for a systematic Review. PROSPERO 2023 CRD42023431233 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023431233.

Review question

Generic question: What type of post-approval evidence development schemes are operating worldwide with respect to high-risk Medical Devices?

The aim is to find and catalog the aims, methods, criteria and procedures used by regulatory authorities worldwide to establish and manage post-approval evidence development schemes for high risk Medical Devices.

Searches

- Databases for published articles:
- MEDLINE
- Embase
- Cochrane
- WoS (Web of Science)
- Databases for grey literature:
- INAHTA and EUNETHTA websites

- Documents from IMDRF and Non-IMDRF members regulatory websites
- Documents from the main HTA agencies that evaluate medical devices (e.g.: NICE, CADTH, FDA, Roszdravnadzor,SFDA, CDSCO, ANDI, other HTA body.)
- Documents from HTA Observatories (e.g.: WHO, NIHR, PAHO, AHWP, ASEAN, APEC, etc.) websites
- Documents from "think tanks" websites (e.g.: OHE, Ossian,)
- Experts in the field will be consulted about other seminal papers that should be included in the review.
- Restrictions:
- Search date: No temporal limitation established Human studies
- Conference abstracts excluded

Types of study to be included

Systematic reviews will be included. Key documents derived by experts in the field. Narrative reviews, conference articles and editorials, and primary studies will be included regarding the relevance of data retrieved.

Condition or domain being studied

Given the limited clinical evidence available for new high-risk medical devices, post-approval evidence assumes a crucial role in facilitating decision-making across the product life cycle. We will review the literature related to post-approval evidence development schemes for high-risk medical devices, in order to identify and synthesize how schemes are operated worldwide with respect to the restrictions or limitations under new medical devices are given a "Certificate of Conformity".

Participants/population

In European Union, under certain circumstances where there is a scarcity of clinical evidence for high-risk devices, notified bodies have the authority to issue certificates of conformity that are subject to specific conditions that mandate the collection of further clinical data within a specified period after the device's initial market entry. In this review we will examine and consolidate information on how post-approval evidence development schemes for high-risk medical devices are implemented worldwide. Specifically, we will focus on understanding the „conditional approval "in other regulatory jurisdictions.

Inclusion criteria:

1. Class III and implantable medical devices or High-risk medical devices.
2. Post-market evidence development schemes established by medical device regulatory authorities' regulation state.

3. Conditional approval/certificate of conformity/Restrictions or limitations.
4. Adverse event reporting schemes.

Exclusion criteria:

1. Non-human studies.
2. Pre-market evidence schemes.
3. Health Technology Assessment reports unless they address Conditional approval/certificate of conformity/Restrictions or limitations of high-risk medical devices.
4. Regulatory bodies from countries which do not template high-risk medical devices legislation.

Intervention(s), exposure(s)

We will consider different classification of medical devices according to their corresponding jurisdictions. We will consider the different regulations available related to high-risk medical devices (according to its references in countries laws) from IMDRF and non-IMDRF.

The interventions are different types of post-approval development schemes for high-risk medical devices (Class III and implantable; MDR – Article 51) in different regulatory jurisdictions.

Comparator(s)/control

Given the focus of the study, it is not considered.

Context

Given the advances on new technologies development worldwide, it is compulsory to endorse regulatory standards for approving medical devices according to scientific and clinical evidence. Since the Medical Device Regulation (EU 2017/745) came into force, the Coordinating Research and Evidence for Medical Devices (CORE-MD) was developed to consider how best to evaluate high-risk medical devices that are implanted into patients, focusing on clinical evaluation and how it can be developed in the EU. Due to the unknown evidence submitted for high-risk medical devices already on the market, because of the confidential activities given among Notified bodies (NBs) and manufacturers, the

CORE-MD group pretend to obtain a frame of reference to determine common certificate of conformity criteria on post-market evidence development for high-risk medical devices.

Main outcome(s)

The main outcomes based on screening results are the following:

- Classification of medical devices in the jurisdictions studied
- Adverse event reporting systems variability

- Post-market evidence development schemes and other limitations or restrictions attached to the certificate of conformity
- Period time established to report an adverse event
- Clinical registries to support post-market surveillance activities
- Re-evaluation/Re-submission procedures and classification of outcomes of re-evaluation

Measures of effect

Taxonomy of aims, methods and procedures used in different jurisdictions worldwide to establish limitations or restrictions on the certificate of conformity.

Additional outcome(s)

1. Classification of medical devices in the jurisdictions studied: According to the jurisdiction studied, we will find their corresponding classification code (e.g.: FDA Medical Device Classification), Class of device (e.g.: Class I, IIa, IIb, III –EU Jurisdiction), Risk level (Low risk, Low-to-medium risk, Medium-to-high risk, High risk – Canada).
2. Post- market evidence development schemes established by regulatory authorities.
3. Adverse event reporting systems: According to the FDA in the USA, the manufacturer, distributor, competitor, healthcare providers and patients have the duty to report medical devices adverse events while in the EU reporting by clinicians are encouraged but not compulsory.
4. Period time established to report an adverse event: e.g.: in the USA and Australia manufacturers need to report the adverse event within 30 days following the date of awareness and within 10 days if the event caused death or serious deterioration in the state of health.
5. Clinical registries to support post-market surveillance activities: The Australian TGA makes information on adverse event reports available in real time through its website and provides formal feedback to stakeholders involved in adverse event reporting.

Measures of effect

Not applicable

Data extraction (selection and coding)

Study selection

The references from the bibliographic search will be classified according to their relation with the inclusion criteria and the adequacy of the study design. Two reviewers will independently screen and select studies for inclusion in the systematic review. The first selection will be carried out by title and abstract, and the second one, by full-text screening. Reviewers will attempt to contact study authors to obtain incomplete data if necessary. Both reviewers will reach an agreement in case of discrepancies. A third reviewer will

participate in the process to resolve them. Researchers won´t be blinded to each other's decisions. Decisions will be electronically recorded in Covidence software.

Data extraction

Data abstraction will be performed according to the different reports obtained from the search strategy. For each eligible study and/or publication suggested by the experts on the field, one reviewer will extract data of interest while a second reviewer will resolve uncertainties. In case of conflicts, to address the discrepancies, a third reviewer will be engaged for resolution. Results will be synthesized and presented in summarized formats such as tables, figures, and/or flowcharts, capturing its essential features.

Risk of bias (quality) assessment

We expect to include heterogeneous documents due to the nature of the topic. Quality assessments of selected studies will be performed by two authors independently using dedicated tools in a second stage. Disagreements between individual judgements will be resolved by discussion. When an agreement is not achieved, the rest of the reviewer team will be invited.

Strategy for data synthesis

We will employ qualitative synthesis methods of the available evidence to describe the differences among the post- marketing evidence and regulations related to the different jurisdictions found in systematic reviews literature. We will summarize study characteristics with respect to the classification systems of medical devices; the conditions and limitations from the market certification (e.g.: CE mark in EU) of High-risk medical devices; the post-market pathway from each jurisdiction to maintain the medical device on market and the schemes developed to that purpose (if these were available). We expect considerably different and heterogenous outcomes among the included studies, therefore we are not going to plan to perform a formal synthesis through meta-analysis.

Analysis of subgroups or subsets

It will be considered regarding the type of information retrieved and its quality.

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Type and method of review

Systematic review

Anticipated or actual start date

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Conflicts of interest

Any author declared conflicts of interest.

Language

English

Country

Spain

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

31 July 2023

Date of first submission

20 July 2023

Details of any existing review of the same topic by the same authors

None

Stage of review at time of this submission

The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and theyunderstand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publicationdetails in due course.

Versions

31 July 2023

31 July 2023

Appendix 2: Search Strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print

In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to May 25, 2023>

Search date: June 12, 2023

Search Strategy:

1 exp "Prostheses and Implants"/

2 (Prosthes?s or Endoprosthes?s or (Implant? adj3 (Artificial or Prosthetic or Prostheses))).tw.

3 ((device? or product?) adj3 (medical or health)).tw.

4 Biomedical Technology/

5 ("Biomedical Technolog*" or (Technology adj3 ("health care" or health))).tw.

6 Biotechnology/

7 Biotechnolog*.ti,ab.

8 ((high-risk or class III or class IIB) adj3 "medical devices").tw.

9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10 *Evidence-Based Medicine/

11 ("Evidence-Based Medicine" or "Evidence-Based Practice").tw.

12 Access to Information/

13 (((Public or Open) adj3 "Access to Information") or "Freedom of Information Act Requests" or "FOIA Request?").tw.

14 Technology Assessment, Biomedical/ec, og, st [Economics, Organization & Administration, Standards]

15 Device Approval/ or Medical Device Legislation/ or Government Regulation/

16 ((approval? adj3 device?) or "food and drug administration device approval" or "food and drug administration device approval process").ti,ab.

17 ("Government Regulation?" or ("Medical Device" adj3 (Legislation or Regulation?))).tw.

18 (evidence adj1 (generation or clinical or development or access or requirement? or 'real-world')).tw.

19 ((condition* adj3 (use? or approval? or apply or evaluation? or shemes or licensing or coverage)) or ((only or approval?) adj1 research)).tw.

20 ((interim or conditional or managed entry) adj3 schemes).tw.

21 (conformity adj3 (assessments or certificate?)).tw.

22 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

23 9 and 22

24 ("letter or case report*" or "historical article*" or (comment or editorial or in vitro or news)).pt.

25 23 not 24

26 Meta-Analysis as Topic/ or meta analy*.tw. or metaanaly*.tw. or Meta-Analysis/ or (systematic* adj (review* or overview*)).tw. or exp Review Literature as Topic/ or cochrane.ab. or embase.ab. or psychlit.ab. or psyclit.ab. or psychinfo.ab. or psycinfo.ab. or cinahl.ab. or "science citation index".ab. or bids.ab. or cancerlit.ab. or "reference list".ab. or bibliography*.ab. or hand-search*.ab. or "relevant journals".ab. or (manual adj1 search*).ab. or "selection criteria".ab. or "study selection".ab. or "data extraction".ab. or "data sources".ab. or (search adj1 strateg*).ab.

27 9 and 25 and 26

28 animals/ not (animals/ and humans/)

29 27 not 28

Embase

Search date: June 12, 2023

Search Strategy:

#30

#29 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

#29

#26 AND #27 AND [humans]/lim

#28

#26 AND #27

#27

'meta analysis'/exp OR ((**meta** NEXT/3 **analy***):ti,ab) OR **metaanalys***:ti,ab OR ((**systematic** NEXT/3 (**review*** OR **overview***)):ti,ab) OR **cancerlit**:ab OR **cochrane**:ab OR **embase**:ab OR **psychlit**:ab OR **psyclit**:ab OR **psychinfo**:ab OR **psycinfo**:ab OR **cinahl**:ab OR **cinhal**:ab OR **'science citation index'**:ab OR

bids:ab OR **'reference lists'**:ab OR **bibliograph***:ab OR **'hand-search*'**:ab OR **'manual search*'**:ab OR **'relevant journals'**:ab OR ((**'data extraction'**:ab OR **'selection criteria'**:ab) AND **review**:pt)

#26

#24 NOT **#25**

#25

'conference abstract'/it OR **'conference paper'**/it OR **'short survey'**/it OR **'abstract report'**/exp

#24

#10 AND #23

#23

#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22

#22

(**conformity** NEAR/3 (**assessments** OR **certificate?**)):ti,ab

#21

((**interim** OR **conditional** OR **'managed entry'**) NEAR/3 **schemes**):ti,ab

#20

((**condition*** NEAR/3 (**use?** OR **approval?** OR **apply** OR **evaluation?** OR **shemes** OR **licensing** OR **coverage**)):ti,ab) OR (((**only** OR **approval?**) NEAR/1 **research**):ti,ab)

#19

(**evidence** NEAR/1 (**generation** OR **clinical** OR **development** OR **access** OR **requirement?** OR **'real-world'**)):ti,ab

#18

'government regulation?':ti,ab OR ((**'medical device'** NEAR/3 (**legislation** OR **regulation?**)):ti,ab)

#17

((**approval?** NEAR/3 **device?**):ti,ab) OR **'food and drug administration device approval'**:ti,ab OR **'food and drug administration device approval process'**:ti,ab

#16

'device approval'/de OR **'medical device regulation'**/de OR **'government regulation'**/de

#15

'biomedical technology assessment'/de AND (**'economics'**/exp OR **'organization and management'**/exp OR **'standard'**/de)

#14

(((**public** OR **open**) NEAR/3 **'access to information'**):ti,ab) OR **'freedom of information act requests'**:ti,ab OR **'foia request?'**:ti,ab

#13

'access to information'/de

#12

'evidence-based medicine':ti,ab OR **'evidence-based practice'**:ti,ab

#11

'evidence based medicine'/de

#10

#1 OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9**

#9

((**'high-risk'** OR **'class iii'** OR **'class iib'**) NEAR/3 **'medical devices'**):ti,ab

#8

biotechnolog*:ti,ab

#7

'biotechnology'/exp

#6

'biomedical technolog*':ti,ab OR ((**technology** NEAR/3 (**'health care'** OR **health**)):ti,ab)

#5

'medical technology'/exp

#4

((**device?** OR **product?**) NEAR/3 (**medical** OR **health**)):ti,ab

#3

prosthes?s:ti,ab OR **endoprosthes?s**:ti,ab OR ((**implant?** NEAR/3 (**artificial** OR **prosthetic** OR **prostheses**)):ti,ab)

#2

bioinstrumentation:ti,ab OR (((**biological** OR **clinical** OR **medical**) NEAR/3 (**instrument*** OR **device?** OR **equipment** OR **apparatus** OR **supplies**)):ti,ab)

#1

'medical device'/exp OR **'prostheses and orthoses'**/exp

WOS (SCI)

Fecha de búsqueda: 12 de junio de 2023

Search Strategy:

20

#18 AND #17 and Editorial Material or Meeting Abstract or Proceeding Paper or Early Access (Exclude – Document Types)

19

#18 AND #17

18

TI=(systematic review) OR AB=(systematic review)

17

#16 AND #6

16

#15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7

15

TI=(conformity NEAR/3 (assessments or certificate?)) OR AB=(conformity NEAR/3 (assessments or certificate?))

14

TI=((interim or conditional or "managed entry") NEAR/3 schemes) OR AB=((interim or conditional or "managed entry") NEAR/3 schemes)

13

TI=((condition* NEAR/3 (use? or approval? or apply or evaluation? or shemes or licensing or coverage)) or ((only or approval?) NEAR/1 research)) OR AB=((condition* NEAR/3 (use? or approval? or apply or evaluation? or shemes or licensing or coverage)) or ((only or approval?) NEAR/1 research))

12

TI=(evidence NEAR/1 (generation or clinical or development or access or requirement? or 'real-world')) OR AB=(evidence NEAR/1 (generation or clinical or development or access or requirement? or 'real-world'))

11

TI=("Government Regulation?" or ("Medical Device" NEAR/3 (Legislation or Regulation?))) OR AB=("Government Regulation?" or ("Medical Device" NEAR/3 (Legislation or Regulation?)))

10

TI=((approval? NEAR/3 device?) or "food and drug administration device approval" or "food and drug administration device approval process") OR AB=((approval? NEAR/3 device?) or "food and drug administration device approval" or "food and drug administration device approval process")

9

TI=("Technology Assessment Biomedical" OR "Device Approval" or "Medical Device Legislation" or "Government Regulation") OR AB=("Technology Assessment Biomedical" OR "Device Approval" or "Medical Device Legislation" or "Government Regulation")

8

TI=("Access to Information" OR "Freedom of Information Act Requests" or "FOIA Request?") OR AB=("Access to Information" OR "Freedom of Information Act Requests" or "FOIA Request?")

7

TI=("Evidence-Based Medicine" or "Evidence-Based Practice") OR AB=("Evidence-Based Medicine" or "Evidence-Based Practice")

6

#5 OR #4 OR #3 OR #2 OR #1

5

TI=(("high-risk" or "class III" or "class IIB") NEAR/3 "medical devices") OR AB=(("high-risk" or "class III" or "class IIB") NEAR/3 "medical devices")

4

TI=Biotechnolog* OR AB=Biotechnolog*

3

TI=("Biomedical Technolog*" or (Technology NEAR/3 ("health care" or health))) OR AB=("Biomedical Technolog*" or (Technology NEAR/3 ("health care" or health)))

2

TI=((device? or product?) NEAR/3 (medical or health)) OR AB=((device? or product?) NEAR/3 (medical or health))

1

TI=(Prosthes?s or Endoprosthes?s or (Implant? NEAR/3 (Artificial or Prosthetic or Prostheses))) OR AB=(Prosthes?s or Endoprosthes?s or (Implant? NEAR/3 (Artificial or Prosthetic or Prostheses)))

Cochrane

Search date: June 23, 2023

Search Strategy:

#1 [mh "Prostheses and Implants"]

#2 (Prosthes?s or Endoprosthes?s or (Implant? NEAR/3 (Artificial or Prosthetic or Prostheses))):ti,ab

#3 ((device? or product?) NEAR/3 (medical or health)):ti,ab

#4 [mh "Biomedical Technology"]

#5 ("Biomedical Technolog*" or (Technology NEAR/3 ("health care" or health))):ti,ab

#6 [mh Biotechnology]

#7 Biotechnolog*:ti,ab

#8 ((high-risk or class III or class IIB) NEAR/3 "medical devices"):ti,ab

#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

#10 [mh "Evidence-Based Medicine"]

#11 ("Evidence-Based Medicine" or "Evidence-Based Practice"):ti,ab

#12 [mh "Access to Information"]

#13 (((Public or Open) NEAR/3 "Access to Information") or "Freedom of Information Act Requests" or "FOIA Request?"):ti,ab 0

#14 [mh "Technology Assessment Biomedical"/ec,og,st]

#15 [mh "Device Approval"] or [mh "Medical Device Legislation"] or [mh "Government Regulation"]

#16 ((approval? NEAR/3 device?) or "food and drug administration device approval" or "food and drug administration device approval process"):ti,ab

#17 ("Government Regulation?" or ("Medical Device" NEAR/3 (Legislation or Regulation?))):ti,ab

#18 (evidence NEAR/1 (generation or clinical or development or access or requirement? or 'real-world')):ti,ab

#19 ((condition* NEAR/3 (use? or approval? or apply or evaluation? or shemes or licensing or coverage)) or ((only or approval?) NEAR/1 research)):ti,ab

#20 ((interim or conditional or managed entry) NEAR/3 schemes):ti,ab

#21 (conformity NEAR/3 (assessments or certificate?)):ti,ab

#22 #10 OR #11 OR #12 OR #13 OR #14 or #15 or #16 or #17 OR #18 OR #19 OR #20 OR #21 64156

#23 #9 AND #22 in Cochrane Reviews

International HTA Database

Search date: June 13, 2023

Search Strategy:

23 #22 AND #9

22 #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR#10

21 (conformity AND (assessments or certificate))[Title] OR (conformity AND (assessments or certificate))[abs]

20 ((interim or conditional or managed entry) AND schemes)[Title] OR ((interim or conditional or managed entry) AND schemes)[abs]

19 ((conditional AND (use or approval or apply or evaluation or schemes or licensing or coverage)) or ((only or approval) AND research))[Title] OR ((conditional AND (use or approval or apply or evaluation or schemes or licensing or coverage)) or ((only or approval) AND research))[abs]

18 ("evidence generation" or "evidence clinical" or "evidence development" or "evidence access" or "evidence real-world")[Title] OR ("evidence generation" or "evidence clinical" or "evidence development" or "evidence access" or "evidence real-world")[abs]

17 ("Government Regulation" or ("Medical Device" AND (Legislation or Regulation)))[Title] OR ("Government Regulation" or ("Medical Device" AND (Legislation or Regulation)))[abs]

16 ((approval AND device) or "food and drug administration device approval" or "food and drug administration device approval process")[Title] OR ((approval AND device) or "food and drug administration device approval" or "food and drug administration device approval process")[abs]

15 "Device Approval"[mh] OR "Medical Device Legislation"[mh] OR "Government Regulation"[mh]

14 "Technology Assessment, Biomedical"[mh]

13 (((Public or Open) AND "Access to Information") or "Freedom of Information Act Requests" or "FOIA Request")[Title] OR (((Public or Open) AND "Access to Information") or "Freedom of Information Act Requests" or "FOIA Request")[abs]

12 "Access to Information"[mh]

11 ("Evidence-Based Medicine" or "Evidence-Based Practice")[Title] OR ("Evidence-Based Medicine" or "Evidence-Based Practice")[abs]

10 "Evidence-Based Medicine"[mh]

9 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

8 ((high-risk or class III or class IIB) AND "medical devices")[Title] OR ((high-risk or class III or class IIB) AND "medical devices")[abs]

7 Biotechnolog*[Title] OR Biotechnolog*[abs]

6 "Biotechnology"[mh]

5 ("Biomedical Technology" or "Technology health care" or "Technology health")[Title] OR ("Biomedical Technology" or "Technology health care" or "Technology health")[abs]

4 "Biomedical Technology"[mh]

3 ((device or product) AND (medical or health))[Title] OR ((device or product) AND (medical or health))[abs]

2 (Prosthes* or Endoprosthes* or (Implant AND (Artificial or Prosthetic or Prostheses)))[Title] OR (Prosthes* or Endoprosthes* or (Implant AND (Artificial or Prosthetic or Prostheses)))[abs]

1 "Prostheses and Implants"[mh]

Appendix 3: Medical Devices Regulations, HTA bodies and other institutions worldwide with a mandate over medical devices (Table 4)

Table 4. Appendix 3: Mapping of regulatory frameworks, regulatory bodies, and HTA bodies worldwide and their role in the access pathway for medical devices

Country (EU member/Non EU member)	Medical Devices Regulation	Regulatory body	Assessment comparing Surveillance / Safety	MD's classification	Adverse event Reporting databasis for HRMD	Health Technology Assessment (Competent authority)	Belonging HTA Network
Argentina	Disposición 96887/2019 administración nacional de medicamentos, alimentos y tecnología médica of 3 December 2019(71)	ANMAT - Administración Nacional de Medicamentos, Alimentos y Tecnología Médica	NO	CLASS I, II, III, IV	Sistema HELENA	IECS - Institute for Clinical Effectiveness and Health Policy	*
Australia	Section 41BD of the Therapeutic Goods Act 1989 (the Act)(72)	TGA - Therapeutic Goods Administration	YES	CLASS I, I-supplied sterile, I-with a measuring	IRIS - Incident Reporting and Investigation Scheme	AHTA - Adelaide Health Technology Assessment ASERNIP-S - Australian Safety	* $ *

				function, IIa, IIb, III		and Efficacy Register of New Interventional Procedures - Surgical PBAC&MSAC - Pharmaceutical Benefits Advisory Committee	 $
Austria (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	AGES - the Austrian Agency for Health and Food Safety	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	BASG - Austrian Federal Office for Safety in Health Care //EUDAMED - European Databasis of Medical Devices	AIHTA - Austrian Institute for Health Technology Assessment UMIT - University for Health Sciences, Medical Informatics and Technology GOeG - Gesundheit Österreich Gmbh/Geschäftsbereich HVB - Hauptverband	* # # * # #

						der Österreichischen Sozialversicherungsträger (Association of Austrian Social Insurance Institutions)	
Belgium (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	AFMPS - Agence Fédérale des Médicaments et des Produits de SANTÉ/FAMHP - Federal Agency for Medecines and Health Products	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	AFMPS/FAMHP Database // EUDAMED - European Databasis of Medical Devices	KCE - Belgian Health Care Centre IPH - Scientific Institute of Public Health RIZIV - INAMI - Rijksinstituut voor Ziekte- en Invaliditeitsverzekering	* # # #
Brazil	Resolução da Diretoria Colegiada - RDC nº 751 de 15/09/2022 (in Portuguese)(73)	ANVISA - Agencia Nacional de Vigilancia Sanitaria/National Health	YES	CLASS I, II, III, IV	ANVISA Database (DATAVISA)	ANS - National Regulatory Agency for Private Health Insurance and Plans	*

		Surveillance Agency				CONITEC - National Committee for Technology Incorporation MoH - Ministry of Health of Brazil	* $ $
Bulgaria (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	IAL - Bulgarian Drug Agency	Not found	CLASS I, II, III, IV	Register of medicinal products authorized for use in the Republic of Bulgaria - IAL Register (Excell) // EUDAMED - European Databasis of Medical Devices	NCPHA - National Center of Public Health and Analyses	#
Canada	MedicalDevicces Regulations SOR/98-282 Current to July 25, 2023(40)	HC - Health Canada	NO	CLASS I, II, III, IV	MedEffect Canada // Government of Canada publications	CADTH IHE - Institute of Health Economics INESS - Institut national d'excellence en santé et en services sociaux	* $ * $ *

						OH - Ontario Health	*
China	Regulations on the Supervision and Administration of Medical Devices (Order No. 739) of 9 February, 2021(42)	CMRO - Chinese Medicine Regulatory Office (Department of Health - the Government of the Hong Kong Special Administrative region) // Taiwan Food and Drug Administration // National Medical Products Administration	YES	RISK CLASS I, II, III, IV	Hong Kong (MDD - Medical Device Division; The List of Medical Devices); Taiwan (Not found); National Medical Products Administration Database (Certificate of a Pharmaceutical Product Database)	CDE - Center for Drug Evaluation, Taiwan	*
Colombia	"DECRETO Nº 4725 DE 2005 (Diciembre 26) por el cual se reglamenta el régimen de registros sanitarios, permiso de comercialización y vigilancia	INVIMA - National Food and Drug Surveillance Institute	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	INVIMA webpage not available	IETS - Instituto de Evaluación Tecnológica en Salud	*

	sanitaria de los dispositivos médicos para uso humano.//Resolución 1405 de 2022 Ministerio de Salud y Protección Social"(74)						
Croatia (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	HALMED - Agency for Medicinal products and medical devices of croatia	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	HALMED Database // EUDAMED - European Databasis of Medical Devices	MIZ - Ministry of Health of the Republic of Croatia CHIF - Croatian Health Insurance Fund CIPH - Croatian Institute of Public Health	# # #
Cyprus (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	CYMDA - Cyprus Medical Devices Authority	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	CYMDA Database (Empty Excell) // EUDAMED - European Databasis of Medical Devices	MoH Cyprus - Ministry of Health of Cyprus	#

Czech Republic (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	SUKL - State Institute for Drug Control	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	SÚKL Database - RZPRO // EUDAMED - European Databasis of Medical Devices	MoH Czech - Ministry of Health of the Czech Republic SUKL - State Insittue for Drug Control	# #
Denmark (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	The Danish Medicines Agency	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	DPSD (Danish Patient Safety Database) // EUDAMED - European Databasis of Medical Devices	DEFACTUM/CFK - Social and Health Services and Labour Market	* #
Estonia (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)// Estonian Medical devices Act (2020) (2)	The Estonian Health Board Terviseamet	NO	CLASS I, CLASS IIa, CLASS IIb, CLASS III	EMDDB (Estonian Medical Devices Database) // EUDAMED - European Databasis of Medical Devices	UTA - Institute of Family Medicine and Public Health	#
Finland (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)//	The Finnish National Supervisory Authority for	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	Fimea (CERE Database) // EUDAMED - European	FinCCHTA - Finnish Coordinating Center for Health	* $ #

	Medical Devices Act (719/2021) (2)	Welfare and Health, Valvira			Databasis of Medical Devices	Technology Assessment	
						FIMEA - Finnish Medicines Agency	#
						THL- National Institute for Health and Welfare	#
France (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	ANSM - The Agence Nationale de Sécurité du Médicament et des Produits de Santé	Not found	CLASS I, CLASS IIa, CLASS IIb, CLASS III	ANSM Database // EUDAMED - European Databasis of Medical Devices	HAS - French National Authority for Health (Haute Autorité de Santé)	* $ #
						AP-HP - Assistance publique-Hopitaux de Paris, FRANCE	*
Germany (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	BfArM - The Federal Institute for Drugs and Medical Devices // DIMDI - The German Institute of Medical	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	DMIDS (German Medical Devices Information and Database System) // EUDAMED - European Databasis of Medical Devices	DIMDI - German Institute for Medical Documentation and Information	#
						GBA - Germeinsamer Bundesausschuss	* #

		Documentation and Information				IQWiG	$ #
Greece (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	EOF - The Greek National Organization for Medicines	Not found	CLASS I, CLASS IIa, CLASS IIb, CLASS III	EUDAMED - European Databasis of Medical Devices	EKAPTY-NKUA - National and Kapodistrian University of Athens	#
						EKAPTY SA - National Evaluation Center of Quality and Technology in S.A.-	#
						EOF - National Organization for Medicines	#
						EOPYY - National Organisation for Healthcare Provision	#
						IFET - Institute of Pharmaceutical Research and Technology	#
						OCSC - Onassis Cardiac Surgery Centre	#

Hungary (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	OGYEI/NIPN - National Institute of Pharmacy and Nutrition	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	OGYÉI List of Restricted Products (updated 27/07/2023 - Excell doc) // EUDAMED - European Databasis of Medical Devices	NIPN - National Institute of Pharmacy and Nutrition SU - Health Services Management Training Center	# #
Indonesia	THE ASEAN (Association of Southeast Asian Nations) Medical Device directive (AMDD) of September 2015(75)	NAFDAC - National Agency for Food and Drug Administration and Control	YES	CLASS I, CLASS II, CLASS III	NAFDAC´s Recalls & Alerts Procedure	CEEBM Center for Clinical Epidemiology-Evidence Based Medicine at Cipto Mangunkusumo Hospital	$
Ireland (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	HPRA/IMB - Health Products Regulatory Authority/Irish Medicines Board	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	HPRA Medical Devices Safety Communications' database // EUDAMED - European Databasis of Medical Devices	HIQA - Health Information and Quality Authority NCPE - National Centre for Pharmacoeconomics, St. James Hospital	* $ # #
Italy (EU)	Regulation (EU) 2017/745 of the European	The Ministry of Health	YES	CLASS I, CLASS IIa,	Medical Devices list's from Ministerio della	AGENAS - National Agency	* #

	Parliament and of the Council of 5 April 2017(2)	Directorate General for Medicines and Medical Devices		CLASS IIb, CLASS III	Salute (csv docs) // EUDAMED - European Databasis of Medical Devices	for Regional Health Services	
						UCSC Gemelli-University Hospital A. Gemelli	$ #
						AIFA - Italian Medicienes Agency	* #
						CRUF/AOUIVR - Centro Regionale Unico sul Farmacia del Veneto	#
						DGFDM IT - Sede del Ministro-Ministero della salute	#
						RER - Regione Emilia-Romagna	#
						UVTA/AOP - Unita di Valutazione Technology Assessment	#
						Veneto/CRUF - Regione Del	#

						Veneto-Area Sanità e Sociale	
Kazakhstan	Order of the Minister of Health of the Republic of Kazakhstan of 30.05.2022 No. KR DSM-49 (76)	NCE - National Centre for Medicines, Medical Devices and Medicinal Equipment Expertise	YES	CLASS 1, CLASS 2A, CLASS 2B, CLASS 3	NCE's Register of Objects of the National Center of Expertise Database	SK-NRCHD - Salidat Kairbekova National Research Center for Health Development	*
South Korea	Ministry of Food and Drug Safety Notification No. 2017-58, July 10, 2017(77)	Ministry of Food and Drug Safety	YES	CLASS I, CLASS II, CLASS III, CLASS IV	Korea´s official medical device information portal website (Safety information>Medical devices subject to recall)	NECA - National Evidence-Based Healthcare Collaborating Agency	* $
Latvia (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	SAMLV - State Agency of Medicines of Latvia	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	Annually State Agency of Medicines Republic of Latvia (Published reports until year 2021) // EUDAMED - European Databasis of Medical Devices	NVD - National Health Service	#

Lithuania (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	VASPVT - State Health Care Accreditation Agency	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	The Institute of Hygiene (HI) - data.gov.lt/reports // EUDAMED - European Databasis of Medical Devices	HI - The Institute of Hygiene VASPVT - State Health Care Accreditation Agency VVKT - State Medicines Control Agency of Lithuania	# # #
Malaysia	The Medical Device Authority Act 2012 (Act 738)(78)	MDA - Medical Device Authority	YES	Class A (low risk), Class B (low to moderate risk), Class C (moderate to high risk) and Class D (highest risk)	(MDA) Medical Device Authority´s recall lists (monthly published) // EUDAMED - European Databasis of Medical Devices	MaHTAS – Health Technology Assessment Section, MoH Malaysia	* $
Malta (EU)	Medical Devices And In-Vitro Diagnostic Medical Devices Provision On The Maltese Market Regulations S.L.458.59 (79)// Regulation (EU)	MCCAA - Malta Competition and Consumer Affairs Authority	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	MMA´s Medical Device Information > National Lists // EUDAMED - European Databasis of Medical Devices	DPA/MoH Malta - Directorate for Pharmaceutical Affairs	#

	2017/745 of the European Parliament and of the Council of 5 April 2017(2)						
Netherlands (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	CIBG FARMATEC - Ministry of Health, Welfare and Sport	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	CIBG FARMATEC - Ministry of Health, Welfare ans Sport (Home>subjects> Warnings from medical device manufacturers>Documents) // EUDAMED - European Databasis of Medical Devices	EUR - Erasmus Universiteit Rotterdam UU - Utrecht University ZIN - National Health Care Institute ZonMw - The Netherlands Organisation for Health Research and Development	# # * $ # *
Norway	Norwegian Laws and Regulations on Medical Devices: act 7 May 2020 no. 37 on medical devices(80); Regulation 9 May 2021 no. 1476 on medical devices(81);	The Norwegian Medicines Agency	YES	CLASS I (Is, Im, Ir), CLASS IIa, CLASS IIb,CLASS III	STATENS LEGEMIDDELVERK (Front page> Notifications from the Norwegian Medicines Agency> Individual files)	NIPH - Norwegian Institute of Public Health HDIR - Norwegian Directorate of Health NIPHNO/nokc - The Norwegian	* # $ #

	Regulation 29 November 2013 no. 1376 on the use of medical devices (82)					Institute of Public Health NOMA - Norwegian Medicines Agency Norwegian Centre for E-health Research	# $
Peru	Ley nº 29459 - ley de productos farmacéuticos, dispositivos médicos y productos sanitarios, Noviembre de 2009(83)	DIGEMID - Dirección General de Medicamentos, Insumos y Drogas	YES	CLASS I, CLASS II, CLASS III, CLASS IV	DIGEMID - Consulta de Registro Sanitario de Dispositivos Médicos	IETSI - Institute of Health Technology Assessment and Research	*
Poland (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	MOH - The Polish Ministry of Health- Office for Registration of Medicinal Products, Medical Devices and Biocidal Products	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	URPL.GOV.PL (List of withdrawn and suspended certificates of comformity> Excell file) // EUDAMED - European Databasis of Medical Devices	AOTMiT - Agency for Health Technology Assessment and Tariff System	* #

Portugal (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	INFARMED - National Authority of Medicines and Health Products	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	INFARMED>Transparency and Publicity Medical Devices' list // EUDAMED - European Databasis of Medical Devices	ACSS IP - Administraçao Central do Sistema de Saùde, I.P. INFARMED - National Authority of Medicines and Health Products	# #
Romania (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	NAMMDR - National Agency for Medicines and Medical Devices of Romania	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	ANMDR web>Important notifications - Medical Devices> Individual files // EUDAMED - European Databasis of Medical Devices	NIPHB - Institutu National De Sanatate Publica (INSP) NSPHMPDB - National School of Public Health, Management and Professional Development UBB - Babes-bolayi University, Cluj School of Public Health	# # #
Russian Federation	Decree of the Government of the Russian Federation	ROSZDRAVNADZOR	YES	CLASS 1, CLASS 2A, CLASS 2B, CLASS 3	ROSZDRAVNADZOR safety monitoring database for Medical devices	CHQA - Center for Healthcare Quality	*

	No. 1416 of 27/12/2012(84)				(according to DECISION 5 No. 174 (December 22), 201 city of Moscow. On Approval of Rules for the Monitoring of Safety, Quality and Efficacy of Medical Products EURASIAN ECONOMIC COMMISSION BOARD). Access not available due to authorissation problems.	Assessment and Control HTA Association	$
Singapore	Health Products Act 2007 (HPA) & Health Products (medical devices) Regulations 2010(85)	HSA - Health Sciences Authority	YES	CLASS A, CLASS B, CLASS C	HSA webpage>MEDICAL DEVICES> FSCA reporting>List of Product Owner`s Field Safety Notices: Before 6 January 2020//On 6 January 2020 or after	ACE - Agency for Care Effectiveness	*

Slovakia (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	ŠÚKL - State Institute for Drug Control	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	EUDAMED - European Databasis of Medical Devices	MoH Slovak Republic - Ministry of Health of the Slovak Republic UniBA FOF - Comenius University in Bratislava	# #
Slovenia (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	JAZMP - Agency for Medicinal Products and Medical Devices of the Republic of Slovenia	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	JAZMP>Medical devices> Vigilance of medical devices> Safety notices> Select Year> Select month // EUDAMED - European Databasis of Medical Devices	JAZMP - Public Agency of the Republic of Slovenia for Medicinal Products and Medical Devices MoH Slovenia - Ministry of Health of the Republic of Slovenia NIJZ - National institue of Public Health	# # #
Spain (EU)	Regulation (EU) 2017/745 of the European Parliament and	AEMPS - Agencia Española de Medicamentos y	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	AEMPS>Comunicación>Notas Informativas>Productos sanitarios //alertasps.aemp	AEMPS - Agencia Española de Medicamentos y	#

	of the Council of 5 April 2017(2)	Productos Sanitarios			s.es // EUDAMED - European Databasis of Medical Devices	Productos Sanitarios AETS-ISCIII - Instituto de Salud Carlos III AETSA - Andalussian HTA Agency AquAS - Agency for Health Quality and Assessment of Catalonia AVALIA FNS - Fundacion Profesor Novoa Santos AVALIA-T - Galician Agency for HTA BIOEF - Basque Foundation for Health Innovation and Research	# * $ # * # * $ # # #

						DGFPS MSPSI - Directorate General for Pharmacy and Health Care Products	#
						FPS - Fundacion Pública Andaluza Progreso y Salud	#
						FUNCANIS - Fundación Canaria de Investigación Sanitaria	#
						IACS - Health Sciences Institute in Aragon, SPAIN	*
						OSTEBA - Basque Office for Health Technology Assessment- Ministry for Health	* $ #
						SESCS - Evaluation AND	#

						Planning Unit-Directorate of the Canary Islands Health Service	
Sweden (EU)	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017(2)	MPA - Medical Products Agency	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	EUDAMED - European Databasis of Medical Devices	SBU - Swedish Agency for Health Technology Assessment and Assessment of Social Services MPA - Medical Products Agency TLV - Dental and Pharmaceutical Benefits Agency	* # # $ #
Switzerland	Medical Devices Ordinance (MedDO) of 1 July 2020 (version: 26 May 2021), SR 812.213 (Not avaliable in English)(86)	SWISSMEDIC - Swiss Agency for Therapeutic Products	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	Not found	SNHTA - Swiss Network for HTA SFOPH - Swiss Federal Office of Public Health	# * $

Tunisia	Not found	DPM - Directorate of and Pharmaceuticals	YES	No official classification system for medical devices	DPM webpage>AMC>AMC Dispositifs Médicaux> Choose among:1)Liste de AMC des Dispositifs Médicaux par Nom Article; 2)Liste des AMC del dispositifs Médicaux par Nom Article; 3)Liste de AMC des Dispositifs médicaux par importaeur; 4) Liste des AMC des dispositifs Médicaux par fournisseur (Not available in english).	INEAS - National Authority for Assessment and Accreditation in Healthcare	* $
Ukraine	Resolution by Cabinet of Ministry of	The Ministry of Health of Ukraine	NO	CLASS I (Is, Im, Ir), CLASS IIa,	Nonexistent	MoH Ukraine - HTA Department of SEC of Ministry	* #

	Ukraine №753 from 02,10,2013(87)			CLASS IIb,CLASS III		of Health of Ukraine	
United Kingdom	Medicines and Medical Devices Act 2021 & 2023 No. 627 The Medical Devices (Amendment) (Great Britain) Regulations 2023(88)	MHRA - The Medicines and Healthcare Products Regulatory Agency	YES	CLASS I, CLASS IIa, CLASS IIb, CLASS III	GOV.UK webpage>Home> Health and social care>Medicines, medical devices> Medical devices regulation and safety>Select Device safety information	HTW - Health Technology Wales HIS - Healthcare Improvement Scotland NICE NIHR AWTTC - All Wales Therapeutics and Toxicology Centre	* $ * $ # * $ # * * $ #
United States	TITLE 21 of The Code of Federal Regulations (39)	U.S. FDA - United States Food and Drug Administration	YES	CLASS I, CLASS II, CLASS III	U.S.FDA webpage>Home> Medical Devices>Medical Device Safety	AHRQ Blue Cross Blue Shield Association CMTP - Center for Medical Technology Policy	* $ $ None

						ICER - Institute for Clinical and Economic Review Kaiser Permanente PCORI (USA)	$ $ $
Uruguay	MERCOSUR/GMC/RES. Nº 25/21 eglamento técnico MERCOSUR de Registro de Productos Médicos (derogación de la resolución GMC N° 40/00)> Decreto del PE N° 428/022 del 27/12/22, publicada en el DO el 20/01/23.(89)	MSP - The Ministry of Public Health	NO	CLASS I, CLASS II, CLASS III, CLASS IV	Nonexistent	HAD - Health Assessment Division, Ministry of Public Health EUnetHTA JA2	* #

Conditional approval of high risk devices: survey of Notified Bodies experiences

Fields marked with * are mandatory.

CORE-MD

Coordinating Research and Evidence for Medical Devices

Medical Device Regulation of high-risk devices: survey of Notified Bodies experiences

The aim of this study is to conduct a survey of NB decisions to investigate and provide insights into the way the regulation on MDs is working in Europe in practice. This unique survey should give us an insight into the "baseline" of how the system currently functions before the MDR is implemented in full, to understand the strengths of the new system early on and identify potential areas for further development.

In the following link you can find the introduction, objectives and methodology of our survey:

Introduction to the Task 3.3 survey of Notified Bodies experiences

The survey has been designed to be self-explanatory and easy to complete. If you note any problems or have any doubts as you are completing the survey, please keep us informed (agnieszka.dobrzynska@juntadeandalucia.es).

*To make the questionnaire easy and not too time-consuming to fill in, each questionnaire has space for one medical device, so please fill in **one questionnaire for each medical device** you would like us to include in this study. If you consider that up to 5 studies of relevance for CE Marking is not enough to give a comprehensive enough picture of the evidence base supporting submissions, or if you would like to suggest any other improvements/amendments to this questionnaire, please do let us know and we will adjust the form.*

QUESTIONNAIRE FOR THE PROSPECTIVE SURVEY

Attributes of the NB evaluating the device

* • **Name of NB**

• **Member of Team-NB?**

- ○ Yes
- ○ No

• **Approximate number of staff (technical and clinical experts employed by the NB)**

• **Location**

• **What do you think are the perceived strengths of your NB?**

- ☐ Cannot answer this question on confidentiality grounds
- ☐ Cost
- ☐ Fast reply
- ☐ Specialization in a particular area
- ☐ Established business relationship with manufacturers in your country
- ☐ Other

• **Do you engage external experts if you do not have in-house experts in a particular area?**

- Yes
- No

DEVICE I

Patient population

- Orthopaedics, traumatology, rehabilitation, rheumatology
- Circulatory system
- Endocrinology and diabetes
- Other

Indication

- **Orthopedics: any component of:**

  - Total hip replacements
  - Partial and total knee replacements
  - Other

- **Diabetes**

  - Implantable products for continuous glucose monitoring
  - Implantable products for drug delivery
  - Non-implantable/external products for drug delivery
  - Other

- **Cardiology**

  - Vascular stents for coronary artery disease
  - Transcatheter aortic valve implantation (TAVI) devices
  - Transcatheter mitral valve repair (TMVR) devices
  - Heart valves for surgical replacement
  - Devices for percutaneus Left Atrial Appendage Occlusion (LAAOc)
  - Leadless pacemaker
  - Subcutaneous implantable cardiac defibrillators (ICDs)
  - Other

(NOTE ABOUT THE ABOVE QUESTION REGARDING THE INDICATION: WE WISH TO MAINTAIN THE CONFIDENTIALITY OF THE DEVICE & MANUFACTURER. HENCE IT IS NOT OBLIGATORY TO ANSWER)

- **Were any clinical studies submitted by the manufacturer as evidence?**

  - Yes
  - No

Evidence submitted by manufacturer, if applicable **(Repeat per studies of relevance for CE Marking; please include studies considered as most relevant in your opinion)**

Study 1

- **Study design**

  - RCT
  - Observational
  - Registry-based randomized trial
  - Other

- **Inclusion of control group**

  - Yes
  - No

- **Sample size (number in the intervention group)**

- **Sample size (number in the control group)**

- **What was the principal end point for performance?**

- **Was the study blinded?**

  - Yes
  - No

- **How was safety evaluated?**

- **Length of follow-up (median, maximum & minimum) (numeric: months)**

  Median follow-up time

Maximum follow-up time

Minimum follow-up time

- Were the principle results reported by study significant? (performance and safety)

Study 2

- Study design

  - RCT
  - Observational
  - Registry-based randomized trial
  - Other

- Inclusion of control group

  - Yes
  - No

- Sample size (number in the intervention group)

- Sample size (number in the control group)

- What was the principal end point for performance?

- Was the study blinded?

Yes

No

- How was safety evaluated?

- Length of follow-up (median, maximum & minimum) (numeric: months)

Median follow-up time

Maximum follow-up time

Minimum follow-up time

- Were the principle results reported by study significant? (performance and safety)

Study 3

- Study design

RCT

Observational

Registry-based randomized trial

Other

- Inclusion of control group

Yes

No

- Sample size (number in the intervention group)

- **Sample size (number in the control group)**

- **What was the principal end point for performance?**

- **Was the study blinded?**

  - Yes
  - No

- **How was safety evaluated?**

- **Length of follow-up (median, maximum & minimum) (numeric: months)**

  Median follow-up time

  Maximum follow-up time

  Minimum follow-up time

- **Were the principle results reported by study significant? (performance and safety)**

Study 4

- **Study design**

  - RCT
  - Observational
  -

Registry-based randomized trial

Other

- **Inclusion of control group**

Yes

No

- **Sample size (number in the intervention group)**

- **Sample size (number in the control group)**

- **What was the principal end point for performance?**

- **Was the study blinded?**

Yes

No

- **How was safety evaluated?**

- **Length of follow-up (median, maximum & minimum) (numeric: months)**

Median follow-up time

Maximum follow-up time

Minimum follow-up time

- **Were the principle results reported by study significant? (performance and safety)**

Study 5

- **Study design**

  - RCT
  - Observational
  - Registry-based randomized trial
  - Other

- **Inclusion of control group**

  - Yes
  - No

- **Sample size (number in the intervention group)**

- **Sample size (number in the control group)**

- **What was the principal end point for performance?**

- **Was the study blinded?**

  - Yes
  - No

- **How was safety evaluated?**

- **Length of follow-up (median, maximum & minimum) (numeric: months)**

  Median follow-up time

Maximum follow-up time

Minimum follow-up time

- **Were the principle results reported by study significant? (performance and safety)**

Cumulative evidence from all studies supporting the dossier

- **What is Notified Body's opinion and considerations on the evidence submitted by manufacturer?**

- **Are there any gaps that still need addressing?**

- **Did the manufacturer claim equivalence with an existing device?**

Yes
No

Role & opinion of expert panel, where applicable

- **Did the expert panel determine there was a need for scientific opinion of an expert panel?**

Yes
No

- **Did this device underwent scrutiny procedure for an expert panel opinion?**

Yes
No

- **If the opinion of the expert panel was provided please supply the corresponding reference/code number**

- **Did the NB agree with the opinion of the expert panel or disagree? (Answer: Agree / disagree)If disagree: what were the reasons:**

- **What further interaction with NB was required? (e.g. Clinical Evaluation Consultation Procedure (CECP), Scrutiny Procedure, Article 55)**

Outcome of conformity assessment

- **Was a CE mark granted**

- ○ **Yes**
- ○ **No**

Restrictions in the conformity assessment

- **What restrictions and limits (as defined in the introduction to this survey and MDR Annex IX) applied on the certificate?**

- ☐ **No restriction**
- ☐ **Restrict intended purpose to certain groups of patients**
- ☐ **Limit on the duration of the certificate**
- ☐ **Undertake specific PMCF studies**
- ☐ **Adapt instructions for use**
- ☐ **Adapt summary of safety and performance**
- ☐ **Other**

- **What happens after restrictions are applied to this CE mark?**

Thank you for taking the time to complete our survey!

Conditional approval of high risk devices: survey of Notified Bodies experiences

Fields marked with * are mandatory.

CORE-MD

Coordinating Research and Evidence for Medical Devices

Survey of Notified Bodies experiences: Medical Device Regulation of high-risk devices:

The aim of this study is to conduct a survey of NB decisions to investigate and provide insights into the way the medical device directives have been applied. This unique survey should give us an insight into the "baseline" of how the system functioned before the MDR was implemented in full, to understand the strengths of the new system early on and identify potential areas for further development.

In the following link you can find the introduction, objectives and methodology of our survey:

Introduction to the Task 3.3 survey of Notified Bodies experiences

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The survey has been designed to be self-explanatory and easy to complete. If you note any problems or have any doubts as you are completing the survey, please keep us informed (agnieszka.dobrzynska@juntadeandalucia.es).

QUESTIONNAIRE FOR THE SURVEY

* **Name of NB**

1. How many certificates of class III and implantable medical devices were issued in total under the Medical Device Directive (MDD) and Active Implantable Medical Device Directive (AIMDD)? Please include certificates issued between 01.08.2012 and 26.05.2021.

2. How many applications for certificates of class III and implantable medical devices were ref used under the Medical Device Directive (MDD) and Active Implantable Medical Device Directive (AIMDD)? Please include applications for certificates rejected between 01.08.2012 and 26.05.2021.

3. How many certificates of class III and implantable medical devices were issued with restrict ions and limitations under the Medical Device Directive (MDD) and Active Implantable Medical Device Directive (AIMDD)*? Please include certificates issued between 01.08.2012 and 26.05.2021.

***Restrictions and limitations as part of the certificate issue may include the manufacturer to: (i) restrict the intended purpose of the device to certain groups of patients or certain medical indications, (ii) impose a limit on the duration of validity of the certificate, (iii), limit the release of the device only to specific post-market clinical follow-up (PMCF) studies, (iv) impose other restrictions in its conformity assessment report, as appropriate.**

4. Without using tradenames or manufacturer details, please describe the device providing its intended purpose, indications and area of medicine, please also describe the type of restriction or limitation that was placed on the certificate considering the information above.

** To answer questions 4, please download, fill in and upload the following document:*

Download

Question_4.docx

Please upload your file(s)

Thank you for taking the time to complete our survey!

Contact

Contact Form

CORE-MD

Coordinating Research and Evidence for Medical Devices

TASK 3.3 Survey to Notified Bodies:

If the NB has issued 1 or more certificates with a restriction or limitation during the survey period, and without using tradenames or manufacturer details, please also describe the type of restriction or limitation that was placed on the certificate considering the information above.

Team NB name: _____

	For which medical devices were certificates with restrictions or limitations issued?	Intended purpose, indication and area of medicine	What was the nature of the restriction or limitation? e.g. (i) restrict the intended purpose of the device, (ii) impose a limit on the duration of validity of the certificate, (iii) limit the release of the device only to specific post-market clinical follow-up (PMCF) studies, (iv) other, please specify.
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Appendix 6: Amstar 2's Quality Assessment

AMSTAR 2 ITEMS	Tarricone et al. 2014	Rey-Ares et al. 2016	Reckers-Droog et al. 2020	Pane et al. 2021	Krüger et al. 2013	Carbonneil et al. 2009	Baeyens et al. 2015
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No	No	No	No	Partial Yes	No
Did the review authors explain their selection of the study designs for inclusion in the review?	No	Yes	Yes	Yes	Yes	No	Yes
Did the review authors use a comprehensive literature search strategy?	Partial Yes	Yes	Yes	Yes	Partial Yes	Partial Yes	No
Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes	No	No	No
Did the review authors perform data extraction in duplicate?	No	No	Yes	Yes	No	No	No
Did the review authors provide a list of excluded studies and justify the exclusions?	Partial Yes	No	No	No	No	No	No
Did the review authors describe the included studies in adequate detail?	No	Yes	Yes	Partial Yes	Partial Yes	No	No
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No	Partial Yes	Yes	No	No	No	No
Did the review authors report on the sources of funding for the studies included in the review?	No	No	No	No	No	No	No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No	No	No	No	Yes	Yes	No
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	No	No	No	No	No	No
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No	No	No	No	No	No	No
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Yes	Yes	Yes	No	Yes	No
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No	No	No	No	No	No	No
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes	Yes	Yes	No	No
GLOBAL QUALITY ASSESSMENT	**Critically Low quality review**	**Critically Low quality review**	**Low quality review**	**Low quality review**	**Critically Low quality review**	**Critically Low quality review**	**Critically Low quality review**

CORE-MD

CORE-MD, Coordinating Research and Evidence for Medical Devices, aims to translate expert scientific and clinical evidence on study designs for evaluating high-risk medical devices into advice for EU regulators.

For more information, visit:

www.core-md.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 965246.