

Recommendations for the safety surveillance of medical devices

Josep M. Pané



**RECOMMENDATIONS FOR THE SAFETY SURVEILLANCE
OF MEDICAL DEVICES**

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Recommendations for the Safety Surveillance of Medical Devices

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To my wife Patricia.

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Chapter 1

GENERAL INTRODUCTION

1. BACKGROUND

Medical devices play a crucial role in healthcare. In the past century, medical device innovation has advanced tremendously and as a result, the life quality and expectancy has increased. A medical device is defined as “any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used for human beings for one or more of the specific medical purpose(s) of diagnosis, prevention, monitoring, treatment or alleviation of disease or injury, investigation, replacement, modification or support of the anatomy or of a physiological process, supporting or sustaining life, control of conception, disinfection of medical devices or providing information by means of in vitro examination of specimens derived from the human body; and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means” (1). The complexity and function of medical devices vary significantly, ranging from bandages or disposable gloves, to more complex forms such as active implants (e.g., pacemakers) and computerized systems.

Recent concerns involving medical devices, such as the metal-on-metal hip implant or the poly implant prosthesis (PIP) scandal, have shown that many questions remain unanswered about the safety of medical devices after market approval, thus highlighting the need for better post-market safety monitoring (2-4).

When compared with other medical products (drugs, cosmetics, etc.) medical devices pose unique challenges in terms of ensuring their safe use. Such challenges include user variability and user learning curves and the technological complexity or permanent nature of some implants (5). Regardless of the challenges associated with the use of medical devices, recent safety issues have led to health authorities questioning the rigor of the current medical device legislation and its ability to rapidly identify new safety issues or monitor known problems in order to protect patients (or its users). This concern further grew after the medical problems that arose when poly implant prosthesis (PIP) breast implants were discovered in patients. The manufacturer (PIP) illegally used industrial silicone instead of medical grade silicone in their implants for many years and lied to the notified body during the annual audits (2, 6). The PIP breast implant scandal in 2012 affected thousands of women and damaged the confidence of the different stakeholders involved in PMS of medical devices (2). More than 400,000 women around the world received PIP implants that were made of industrial-grade silicone gel, prone to rupture, leading to inflammation and irritation.

Another incident in 2012 involving hip implants raised a public health concern: metal-on-metal (MoM) hip replacements were successfully implanted, but metal abrading against metal

caused erosion and leaking of metal particles into soft tissue. This resulted in thousands of patients around the world being exposed to high levels of toxic metals from failing hip implants. The chromium and cobalt ions from the MoM hip implants could get into the tissues of patients with this type of hip implants, leading to reactions that damaged the muscle and bone, and led to revision procedures, or left some patients with long term disability (7, 8). This safety issue was only identified by the Australian Health Authorities upon review of the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR), and this finding was confirmed by the National Joint Replacement Registry of England, Wales, and Northern Ireland (NJR) and the New Zealand Registry. This resulted in a worldwide recall of the MoM hip implants. The safety issue was highly publicized as MoM hip implants were approved for market use although data derived from clinical trials was lacking. Additionally, the manufacturers did not systematically review post-market clinical data (including device registries containing post-market surveillance information) and thus failed to identify and report this risk to the Health Authorities (4, 9-11).

In addition to these two examples, there have been other safety issues associated with other implantable medical devices (e.g; Sprint Fidelis leads, Riata leads and Björk Shiley heart valves) that were not identified during the pre-market safety assessment, and were only identified during the PMS phase (12-14). The consequences of these safety issues may lead to product recalls, which have significant repercussions to patient's health. If an explant surgery is required to replace a defective medical device, the risks associated with this type of surgery must be weighed against the risks of occurrence of medical device malfunction. For example, in the case of Björk Shiley heart valves, this particular type of heart valve had a risk of fracture, leading to death in two thirds of the events. The valve was recalled and class actions by affected patients and families followed.

It is also important to take into consideration that medical device related injuries are not necessarily caused by failures of the medical device itself. The design of a medical device plays a key role when evaluating possible errors that may arise while using the product. The reason behind some medical device errors may be associated with a lack of training. To minimize such errors, user trainings should focus on more effective error prevention strategies such as retraining users during the medical device label review, and verifications during the critical steps of the medical device use (15).

For all the reasons mentioned above, worldwide medical device regulations are undergoing ongoing changes geared towards improving the processes of new medical device development and post-market surveillance (16-18).

2. NOVEL MEDICAL DEVICE DEVELOPMENT

The novel medical device development pathway is an iterative development cycle where continuous amendments and design incremental improvements are performed based on feedback from physicians/users, technology developments, preclinical testing, manufacturing improvements and clinical experience. After receiving such feedback, ideas are transformed into prototypes, which are again tested, re-assessed, optimized and then finalized (figure 1) (19). An example of this development cycle is the invention of the first intraocular lens (IOL). Sir Harold Ridley was the first to successfully implant an IOL on 29 November 1949. Inspired by one of his interns, Sir Ridley developed the idea of implanting an intraocular lens (20). During World War II Sir Ridley treated Royal Air Force pilots who had fragments of shattered cockpit in their eyes. He learnt that the acrylic plastic material of the cockpit did not lead to any long-term damages of the eye. This finding explains why he picked the acrylic plastic material for his new invention, the first IOL. Soon after Sir Ridley's discovery, several manufacturers adapted his new idea to rapidly produce similar IOLs with improved characteristics.

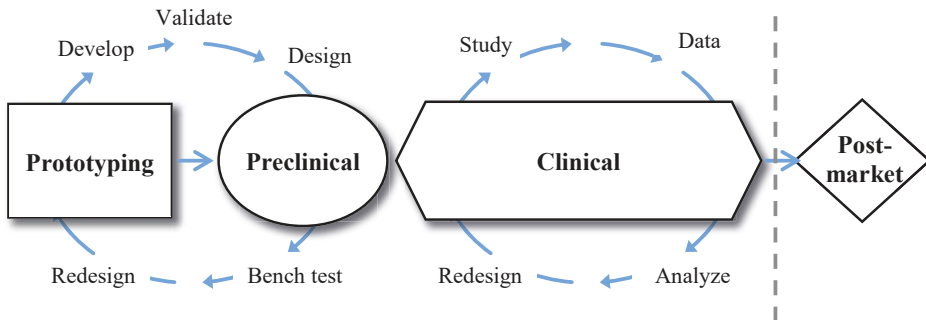


Figure 1: Medical device iterative development cycle

After the initial discovery phase of a medical device, pre-clinical testing starts. Medical devices that consist of materials that are biocompatible with human tissue, such as acrylic plastic (used by Sir Ridley), stainless steel or ceramic (21) do not require animal testing. They do not pose any new safety risks that could not be assessed using the available resources such as risks and failure modes associated with the novel medical device, risks commonly attributed to this general device type, and PMS information for similar marketed devices. Although a great amount of information is obtained from pre-clinical testing, clinical trials may be required in certain circumstances. If the biocompatibility and safety of medical devices cannot be assured during preclinical testing, clinical trials must follow. An example includes some high risk medical devices like pacemakers (22). This is a consideration to be made on a product by product basis and depends on the medical device materials, components, clinical procedures, characteristics of the anatomical site where the medical is to be implanted (in the case of im-

plants) or target populations. However, for most of the medical devices, extrapolating clinical data from published clinical investigations or other studies of similar devices in the scientific literature, or from clinical experience of a similar device may be sufficient to obtain approval to market at least in most countries (Figure 2). For those medical device that require clinical studies to obtain regulatory approval, the studies are usually small (number of patients <500 on average) (22).

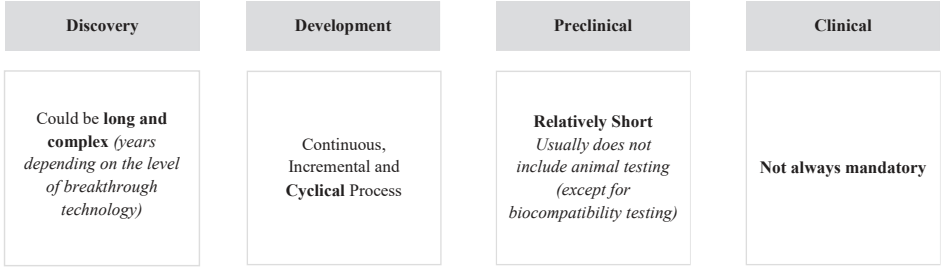


Figure 2: Medical device development phases

For medical devices, the amount of clinical data required to obtain the market approval is not clearly defined, and the type of information that is considered acceptable as clinical data differs depending on the regulatory approval system. Comparing the EU to the US, the EU medical device regulatory system differs from that in the US but both systems have key similarities; both systems have a marketing authorization path through demonstration of equivalency with existing, comparable devices and a pre-market approval (conformity assessment procedure) path for high-risk devices; the most strictly regulated medical devices (23-25). In the US a pre-market approval by the Food and Drug Administration (FDA) is required, although non-significant modifications to a medical device already introduced to the market could be approved through shorter supplemental procedures (26). In Europe, conformity to the essential requirements from the EU regulation is required (18), and in case of high-risk devices such as pacemakers and hip prostheses, an assessment of conformity by a notified body is required. Providing clinical data is part of both procedures, but the type of information considered as acceptable clinical evidence varies (27).

After completing the clinical phase (if required), the manufacturer moves to obtain the market approval. In some jurisdictions, medical devices do not require a formal approval from the health authority (for example, in the EU some low-mid level risk medical devices can be placed on the European market via self-certification). As part of the risk analysis, a manufacturer is required to identify all risks or hazardous situations associated with the medical device before placing a medical device on the market. The manufacturer must meet a risk level that is as low as possible. Any residual risks should be mitigated using risk mitigation activities (system messages on the medical device itself, instructions to the user in the Directions For Use etc.),

and acknowledged in the risk management documents. The overall risks associated with the medical device should be reduced as far as possible and should be acceptable when weighed against the benefits. Due to the nature of medical devices, some risks and hazardous situations may not be identified or completely defined during the pre-market phase, and some risks may only be characterized during the post-market period when medical devices are used in real life, in larger populations, and for a longer period of time (28). This is the reason why having a robust risk management process throughout the whole lifecycle of the product evaluating the data collected during post-market surveillance is vital to assess the safety profile of the medical device.

3. POST-MARKET SURVEILLANCE

After the discovery, development, preclinical and clinical testing phases have been successfully completed, the medical device is licensed for marketing and enters the Post-Market Surveillance (PMS) phase. PMS is defined as the systematic process to collect and analyse experience gained from medical devices that have been placed on the market (1). PMS activities ensure that PMS data are analysed and used to support decisions about the safety and performance of a medical device. PMS also has the potential to generate real-world evidence that can be used either to obtain new marketing authorizations for the medical device (new markets, new indications supported by actual use of the medical device), or of the next generation of medical device (29). This information obtained from post-market surveillance can also identify new opportunities for improvement associated with the medical device, and provides input into the design and development processes (1), and into the risk management process (30).

As part of the risk management process for medical devices, a manufacturer is required to compile a list of all known risks and foreseeable hazards associated with the medical device, including any risks associated with failure in the manufacturing and assembling of components as well as any risks associated with the misuse of the device. The risk management requirements to obtain the medical device market approval focus on a safe medical device design that has a risk level as low as possible. Any residual risks need to be mitigated if possible by medical device alarms that function as protection against a device failure during its use, and if this is not feasible (e.g. for implantable medical devices) those risks should be mentioned in the product labeling (e.g. user manual, directions for use). The risk management documents of the medical device must be continuously updated, also in the post-market phase, using the safety data collected during PMS (30).

There is a wide range of sources of PMS information (figure 3). The current system of PMS primary relies on passive PMS data sources (31). Passive post-market data sources such as

spontaneous reports are easily accessible and well established. However, this type of PMS data source has the following limitations: underreporting due to different reasons including lack of time or fear of consequences if errors are the root cause, uncertainty about the medical device causing the adverse event, difficulty in accessing reporting forms, lack of awareness of the requirements for reporting, and lack of understanding of the purpose of the Spontaneous Reporting Systems (SRS) (32), over-reporting where medical devices with well-known adverse event/product problems are more likely to be reported than other medical devices based on influence from social network, media coverage or litigation effects, missing and incomplete data, or duplicated reporting (33, 34). Alternatively, proactive PMS data sources for medical devices such as post-market clinical follow-up (PMCF) studies, medical device registries, literature review, and other proactive PMS data sources, are key data sources to strengthen the PMS for medical devices but are still underdeveloped and underused.



Figure 3. Sources of PMS information

Global regulations mandate medical device manufacturers to develop and maintain a systematic procedure to review experience gained from the post-market phase, and to implement appropriate means to apply any necessary corrective action. Unfortunately, most of the worldwide medical device regulations do not provide any guidance on how this requirement should be implemented (31). The new regulatory initiatives aim to strengthen the key aspects of the PMS system while enforcing new requirements (e.g. Post-Market Surveillance (PMS) plans, Periodic Safety Update Reports (PSURs), Post-Market Clinical Follow-up (PMCF) plans) to build a more proactive system for the safety evaluation of medical devices. (35,36). The new proactive system should be correctly designed to allow for early detection of possible malfunctions and/

or complications of medical devices that may occur, and implement appropriate risk minimization measures. Today, many medical device manufacturers have a reactive PMS system that is based on the collection of post-market data received from spontaneous reporting of complaints and incidents. Unfortunately, few proactive PMS processes have been designed to actively gain knowledge on the safety and performance of the medical device through external sources like registries, social networks, and literature.

4. UNIQUE CHALLENGES OF SURVEILLANCE OF MEDICAL DEVICES

Before embarking on a mission to change the current system of surveillance of medical devices, one needs to understand the peculiarities of this system including the factors contributing to adverse events, and current challenges that are associated with the lack of global alignment on PMS requirements and guidelines for processes and tools.

4.1. Factors contributing to adverse events

As previously noted, the design of a medical device and errors related to the use of the medical device are two key factors that play a crucial role when evaluating contributing factors to adverse events. Many of these could be minimized with more user-friendly designs of medical devices and adequate training. User training is one of the most important risk mitigation strategies for medical devices. These factors influence the safety assessment performed during the development and the post-market phase of a new medical device (37).

4.2. Safety data sources

Databases and registries that capture data on the medical devices and their recipients are a key aspect in the post-market surveillance process. As previously mentioned, prospective data sources like medical device registries are underused. Different medical device registries in various therapeutic areas (orthopedic, vascular, cardiac, ophthalmic) currently exist (38-43). Medical device registries have the advantage to not be restricted to patients experiencing medical device malfunctions or adverse events. Data in medical device registries, which is collected during routine clinical practice, offers a different angle and a denominator, making them a more appropriate data source to calculate event rates. However, most of the data currently used for surveillance of medical devices is still obtained from spontaneous reporting systems. Limitations with SRS such as underreporting and lack of quality of safety data make it difficult to ensure the timely detection of safety issues (33). There are different national SRS, but in contrast to what is available for drugs (Vigibase from the WHO), no global database to access global spontaneous reports currently exists. These challenges make the signal detection process more complex and less efficient.

4.3. Safety evaluation tools

A robust post-market surveillance system requires procedures and guidance as well as consistent use of safety evaluation tools to ensure the timely detection and evaluation of possible safety issues associated with a specific medical device. In the past, such tools did not exist. Recently, some new safety evaluation tools have been required as part of the new EU MDR; PSURs, PMS plans, PMCF plans. However, these new safety evaluation tools are not required globally across other jurisdictions making it more difficult to ensure consistency in the standards applied across the safety evaluation process. Due to this lack of uniformity, timely detection of safety issues is still a challenge.

4.4. Standardization and harmonization

Another challenge associated with the surveillance of medical devices is the heterogeneous nature of reporting requirements across jurisdictions. Inconsistency in post-market reporting requirements leads to different levels of completeness that makes comparisons between different SRS databases difficult. The most significant challenge is the exemption applications in the EU (amongst other exemptions, expected side-effects are not reportable in EU but subject to event trending (18)), in Canada (44) and in Australia (45), however, no exemptions are applicable in the US (46). Furthermore, the lack of a harmonized global standard data set for reporting makes integration of data from different databases challenging (5, 47).

The safety data collection process is subject to additional obstacle, which differ depending on the country requirements. Additionally, different adverse event coding dictionaries and unique device identification repositories used for the signal detection of medical devices exist depending on the jurisdiction. This lack of standardization and harmonization leads to complications during the signal detection process and the subsequent delayed generation of safety signals.

5. AIMS AND OUTLINE OF THIS THESIS

This thesis aims to present an overview of the current PMS system for medical devices, and explores potential enhancements from a technical and a regulatory perspective.

The thesis is divided into seven chapters. The first chapter provides a general introduction and context to the field of post-market surveillance of medical devices. In Chapter 2 we compare the process and methodology used in the assessment of the safety profile of medical devices with that of medicines in order to identify potential gaps and make recommendations for the adoption of new approaches and methodologies in the medical device context. In Chapter 3 we performed a case study and conducted a descriptive analysis of the PMS data from one of the most important publicly available spontaneous reports database; the Food and Drug

Administration's (FDA) Manufacturer and User Facility Device Experience (MAUDE). We assess the quality and the quantity of these spontaneous reports using MRA hip implants as a proof of concept.

In Chapter 4 we present one of the key processes to ensure an efficient PMS system; namely the safety signal detection. We describe the different aspects influencing the signal detection related to medical devices in order to identify potential gaps and to make a recommendation for the adoption of new standardized and harmonized policies or early detection of risks associated with medical device use.

In Chapter 5 the authors explore the use of new tools for the PMS of medical devices. We describe the new EU Regulation on PMS of medical devices, and provide recommendations on how to implement the new requirement for a PMS plan.

In Chapter 6 we explore the use of blockchain and how this new technology could support the ongoing efforts to improve the PMS system for medical devices. Finally, a summary discussion and future perspectives are presented in Chapter 7.

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CHAPTER 2

SAFETY SURVEILLANCE SYSTEM OF MEDICAL DEVICES COMPARED TO MEDICINES

2.1.

Evaluating the Safety Profile of Non-Active Implantable Medical Devices Compared to Medicines

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premarket surveillance, post-market surveillance, risk management, safety evaluation

ABSTRACT

Recent safety issues involving non-active implantable medical devices (NAIMDs) have highlighted the need for better premarket and post-market evaluation. Some stakeholders have argued that certain features of medicine safety evaluation should also be applied to medical devices. Our objectives were to compare the current processes and methodologies for the assessment of NAIMD safety profiles with those for medicines, identify potential gaps, and make recommendations for the adoption of new methodologies for the ongoing benefit–risk monitoring of these devices throughout their entire life cycle. A literature review served to examine the current tools for the safety evaluation of NAIMDs and those for medicines. We searched MEDLINE using these two categories. We supplemented this search with Google searches using the same key terms used in the MEDLINE search. Using a comparative approach, we summarized the new product design, development cycle (preclinical and clinical phases), and post-market phases for NAIMDs and drugs. We also evaluated and compared the respective processes to integrate and assess safety data during the life cycle of the products, including signal detection, signal management, and subsequent potential regulatory actions. The search identified a gap in NAIMD safety signal generation: no global program exists that collects and analyzes adverse events and product quality issues. Data sources in real-world settings, such as electronic health records, need to be effectively identified and explored as additional sources of safety information, particularly in some areas such as the EU and USA where there are plans to implement the unique device identifier (UDI). The UDI and other initiatives will enable more robust follow-up and assessment of long-term patient outcomes. The safety evaluation system for NAIMDs differs in many ways from those for drugs, but both systems face analogous challenges with respect to monitoring real-world usage. Certain features of the drug safety evaluation process could, if adopted and adapted for NAIMDs, lead to better and more systematic evaluations of the latter.

KEY POINTS:

- The collection of safety information and its integration into the risk management process for medical devices is not consistent.
- Collaboration between all stakeholders is needed to develop a more proactive safety evaluation process.
- This new process should incorporate real-world data to develop a risk assessment model that is suitable for all medical devices.

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1. INTRODUCTION

Medical devices play an increasingly important role in healthcare worldwide. A medical device is defined as “any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease, replacement or modification of the anatomy or of a physiological process, and control of conception”. Unlike a drug, a medical device does not achieve its principal intended action in the human body by pharmacological, immunological, or metabolic means, but it may be assisted in its function by such means (1). Medical devices are classified into different categories depending on the risk of harm that comes with their use. The dimension, complexity, and function of medical devices vary significantly, ranging from bandages, disposable gloves, and wheelchairs to more complicated forms such as active implants (i.e., pacemakers) and computerized systems used in cataract surgery.

This paper focuses on non-active implantable medical devices (NAIMDs) and uses these as a proxy to extrapolate the conclusions of the research, where possible, to other types of medical devices. An implantable medical device is one that is partly or totally inserted into the human body or a natural orifice and expected to stay there for 30 days or more or that is used to replace an epithelial surface or the surface of the eye and is expected to stay in use for 30 days or more. Examples of implantable medical devices include dental implants, breast implants, hip implants, or intraocular lenses. Both insertion or application and removal of implantable medical devices requires surgical or medical procedures. To be classified as an NAIMD, the medical device must not have an integral power source (2). All NAIMDs fall into the European medical device risk class IIb and III.

Recent concerns involving NAIMDs, such as the Poly Implant Prothese (PIP) breast implant (3) and the metal-on-metal hip implant, have shown many questions remain about the safety and effectiveness of NAIMDs after market approval, thus highlighting the need for better post-market monitoring. When compared with medicines, medical devices pose unique challenges in terms of ensuring their safe and effective use. Such challenges include user variability and user learning curves and the technological complexity or permanent nature of some implants. This latter challenge is mainly a potential problem with regard to safety and less with regard to effectiveness. In fact, the effectiveness of implantable devices is usually higher than that of drugs because implantable devices, in contrast to drugs, do not suffer from patient non-adherence.

To address this need for improvement, some stakeholders have argued that certain features of drug regulation should be applied to medical devices. This entails the recommendation or opinion that NAIMDs should undergo an assessment of their benefit–risk profile prior to

being placed in the market—as well as continuous safety surveillance monitoring throughout the product life cycle. However, adoption of the medicinal product benefit–risk evaluation framework in its entirety may be difficult because of the significant differences between medicines and NAIMDs.

For all the reasons mentioned above, worldwide medical device regulations are undergoing ongoing changes geared towards improving premarket and post-market evaluations of device safety.

In this paper, we compare the processes and methodologies used in the assessment of the safety profile of medical devices with those for medicines to identify potential gaps and make recommendations for the adoption of new approaches and methodologies in the medical device context. To make this comparison more practical, we used a specific group—NAIMDs, rather than the entire spectrum of medical devices—as an example.

2. LITERATURE REVIEW METHODOLOGY

A literature review served to examine the current tools for the safety evaluation of NAIMDs and medicines. We searched MEDLINE using these two categories. We supplemented this search with Google searches using the same key terms used in the MEDLINE search.

3. SAFETY EVALUATION: A LIFE-CYCLE APPROACH

For both medicines and NAIMDs, the goal is to evaluate safety throughout the entire life cycle of the product. The way this is done differs substantially between the two. To understand the differences between the safety evaluations, it is important to focus on the different types of adverse events and to evaluate the factors contributing to these adverse events. The differences and similarities between medicines and NAIMDs are shown in Fig. 1.

The design of a NAIMD plays a key role when evaluating possible errors that may arise while using the product. A study involving healthcare employees from three hospital systems indicated that a lack of training is associated with most errors. To minimize such errors, user training should focus on more effective error-prevention strategies such as retraining of the user during the NAIMD label review and double checks during critical steps of NAIMD implantation (4).

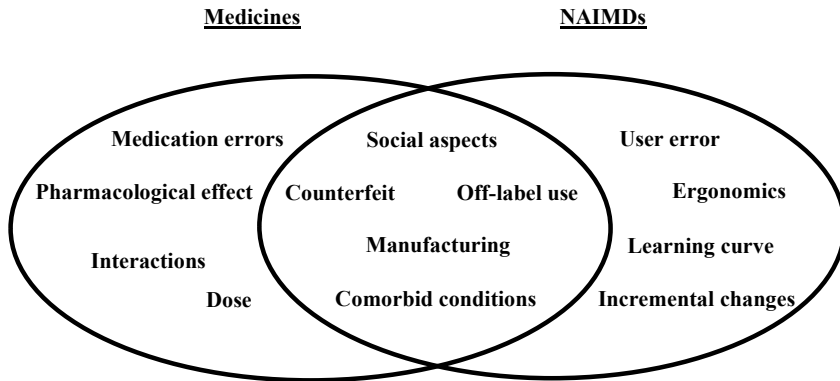


Figure 1. Factors contributing to adverse events: Medicines and non-active implantable medical devices (NAIMDs).

The three main causes of adverse events have been found to be user challenges, design problems, and lack of effective training; many of these could be minimized with adequate training and more user-friendly medical devices.

For medicines, the factors contributing to adverse events are mostly pharmacological effect, medication errors, drug interactions, and incorrect dosing.

These differences in factors contributing to adverse events influence the safety assessment performed during development and the post-market phase of a new product. Some metabolic conditions could contribute to adverse events for special populations for medicines. For NAIMDs, other characteristics such as anatomical differences-particularly in size-need to be considered.

3.1. New Product Development

The premarket safety assessment for both NAIMDs and medicines is a process that comprises in-depth planning, evaluation, and reporting throughout the development of the product: from discovery and development to preclinical and clinical testing.

3.1.1. Discovery

The NAIMD pathway starts with the creation of a new product. Once the NAIMD has been ideated, the new prototype enters the iterative development cycle where continuous amendments and incremental design improvements will be made based on feedback from physicians/users, technology developments, preclinical testing, manufacturing improvements, and clinical studies. After such feedback, new ideas are transformed into prototypes, which are again tested, re-done, optimized, and then finalized. In contrast, during the discovery of new medicinal products, many compounds are generated with the objective of detecting the best candidates

for further development. The candidate drugs are frequently selected using in vitro testing models and enter formulation development in a continuous and unidirectional process.

In 1964, Sir James W. Black developed the first clinically important beta blocker, propranolol, revolutionizing the medical treatment of angina pectoris (6). Beta blockers have been a key contribution to clinical medicine and pharmacology in the twentieth century. Following Sir Black's breakthrough, other beta blockers were developed as medicines.

Another type of product innovation, also through breakthrough technology, is the modification of the structure of existing products. This innovating process is more rapid for medical devices than for medicines. In general, modifying the molecular structure of an existing medicinal product to obtain a new medicinal product involves a long and protracted process, whereas the incremental changes made to medical devices can be released to the market much faster. A new medicinal product will have to undergo mandatory preclinical and clinical trials prior to approval and market authorization, whereas this is not always required to place a device in the market.

3.1.2. Development

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3.1.3. Preclinical

After the ideation and development phases, the preclinical testing starts. For medicines, candidates not excluded in the initial steps are tested for efficacy and safety in animals. These animal studies are planned to ascertain a safe dose with which to start studies in humans, to learn which organs may be more affected by potential toxic effects, and to understand pharmacokinetic and dynamic parameters. Manufacturers of NAIMDs and medicines are required to test the safety of the new products via ex vivo and in vivo studies. The role of animal testing for NAIMDs differs significantly from that of medicines. Contrary to the process with medicines, where all new products require organ-specific animal models, the majority of new NAIMDs

do not require animal testing because they often use materials that are biocompatible with human tissue, such as stainless steel or ceramic. However, some devices with novel materials (i.e., materials that have not previously been used in a marketed medical device with the same type and duration of contact) might require biocompatibility testing in animals (7).

3.1.4. Clinical

Although a large amount of information is obtained from animal testing, this is not sufficient to rule out human trials. No animal or in vitro testing is sufficiently comparable to that in humans; human trials are inevitably required for medicines. For NAIMDs, clinical trials are used only in certain circumstances, for example when the biocompatibility and safety of NAIMDs cannot be assured during preclinical trials (both ex vivo and in vivo) (Fig. 2). This is considered on a product-by-product basis and depends on the NAIMD materials, components, clinical procedures, characteristics of the anatomical site for implantation of the NAIMD, or target populations.

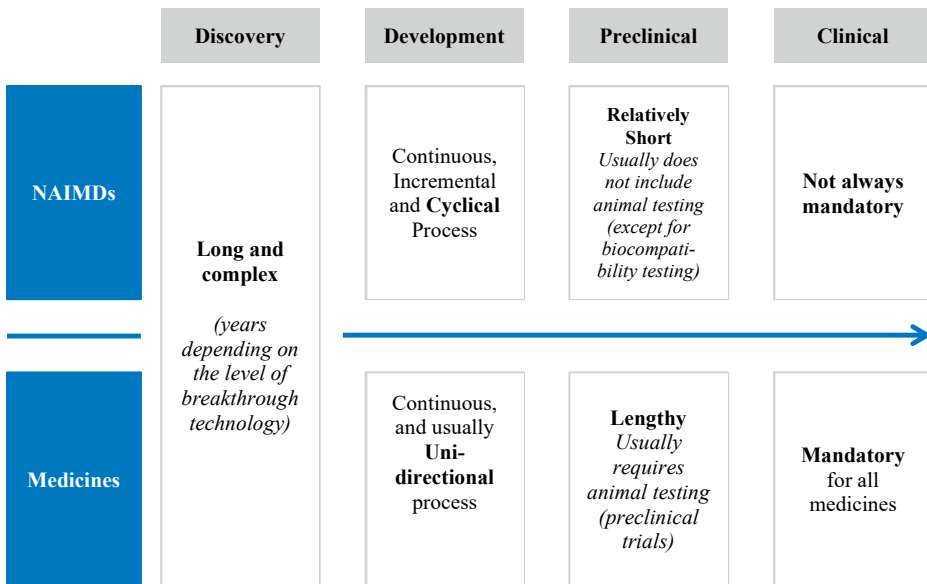


Figure 2. Overview of the main differences during new product development between non-active implantable medical devices (NAIMDs) and medicines

Therefore, for some NAIMDs, unlike for medicines, extrapolating clinical data from published clinical investigations or other studies of similar devices in the scientific literature, or from clinical experience of a similar device may be sufficient to obtain approval to market at least in most countries. For NAIMDs that require clinical studies to obtain regulatory approval, the studies are usually smaller (average number of patients: \500) than pharmaceutical clinical trials, which are ruled by the size required to show efficacy (8). The technical aspects of medical

devices make it difficult to decide how much clinical data are required for a new NAIMD: substantially equivalent NAIMDs, and those with a completely new design or indication will all require different ways of evaluating NAIMD safety. For NAIMDs, the amount of clinical data required to obtain the market approval is not clearly defined.

As can be seen in Fig. 3 (9, 10), safety assessment for NAIMDs is an iterative process of detecting, assessing, managing, and communicating the benefits and potential risks while the product is not yet approved. Although the premarket safety assessment for medicines could be iterative, it is often unidirectional rather than cyclical.

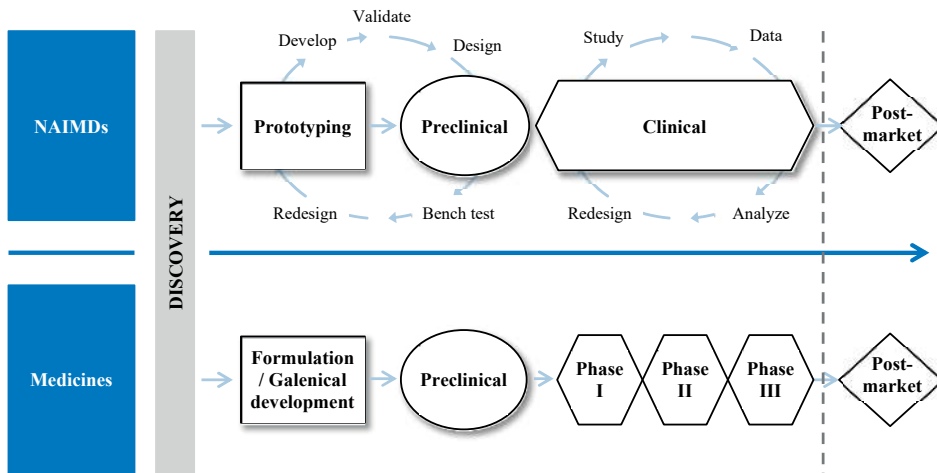


Figure 3. The medicinal product and the non-active implantable medical device (NAIMD) development pathway

3.2. Post-market surveillance

After the discovery, development, and preclinical and clinical testing phases are successful, the product is licensed for marketing and enters the post-market phase. Different types of data related to the actual use of the product are collected, and these post-market data are integrated into the risk management plan (RMP) of the product. The data collection processes and the integration of such data are similar but differ in some aspects between NAIMDs and medicines.

3.2.1. Importance of data sources

Data sources are a key aspect in the safety evaluation process. It is important to consider the different post-market surveillance data sources and their limitations. Table 1 provides examples of types of post-market data sources for both NAIMDs and medicines.

Table 1. Examples of post-market data sources for NAIMDs and medicines

	NAIMDs	Medicines
Spontaneous Reports	<ul style="list-style-type: none"> MAUDE (FDA), MEDSUN (FDA), MHRA (UK) 	<ul style="list-style-type: none"> AERS (FDA), EudraVigilance (EEA), VigiBase (WHO)
Patient Registries	<ul style="list-style-type: none"> SCAAR, EUREQUO, AOANJRR 	<ul style="list-style-type: none"> ESID, Atassia Teleangiectasia (Italy)
Prescription Databases	<ul style="list-style-type: none"> Underdeveloped 	<ul style="list-style-type: none"> The Intensive Medicines Monitoring Programme (New Zealand), NorPD
Claims Data Sources	<ul style="list-style-type: none"> Medicare & Medicaid (US) 	<ul style="list-style-type: none"> FDA Sentinel, Medicare & Medicaid (US)
Electronic Medical Records (EMR) Databases	<ul style="list-style-type: none"> Underdeveloped 	<ul style="list-style-type: none"> EUADR, FDA Minisentinel, General Practice Research Database (UK)
Public Information on Safety Issues	<ul style="list-style-type: none"> Medical Device Safety (FDA), Catalan Agency for Health Technology Assessment and Research 	<ul style="list-style-type: none"> CDER (FDA), PRAC (EMA)
Post-Authorization Studies	<ul style="list-style-type: none"> Post-market Clinical Follow-up Studies (EU), Post-Approval Studies (US), 522 Studies (US) 	<ul style="list-style-type: none"> Interventional study (efficacy study, PASS, PAS) and non-interventional study (efficacy study, PASS, PAS)

Many data sources are common to both products, but some have been explored more in one than in the other. For both NAIMDs and medicines, passive post-market data sources are easily accessible and well established. On the other hand, active data sources are further advanced for medicines than for NAIMDs.

The main differences between NAIMDs and medicines is that prescription or pharmacy dispensing and electronic medical records (EMRs) or claims databases for NAIMDs are underdeveloped. This is primarily because of the lack of a unique device identifier (UDI). UDIs will enhance post-market surveillance activities by providing a standard and unambiguous way to document device use in EMRs or healthcare utilization databases.

The integration of the UDI into such databases could potentially support public health-related activities such as reducing use errors and the reporting and assessing of adverse events and other problems related to the NAIMD. It would also enable tracking of product withdrawals, assessment of patient outcomes and risk–benefit profiles of NAIMDs across different populations, as well as provide a viable source of device identification information to the various stakeholders.

Integrating UDI information into such databases will increase the use of ‘real-world’ data in the decision-making process. The US FDA has indicated that establishing a medical device safety evaluation system to gain real-world evidence is one of its strategic priorities for 2016–2017. In Europe, on 25 May 2016, an agreement was reached with the European parliament representatives, and the UDI will become reality in the near future (11). This evidence will then

aid in the regulatory decision-making process. The new system aims to lead to a better and faster identification of safety signals by collecting post-market data in a timely manner. Today's vast amount of electronic clinical data will be used to determine safety signals and support risk-benefit analysis when the quality of data can be guaranteed and advanced analytics can be applied (12).

3.2.2. Risk Management

In the life cycle approach new safety data needs to be included in the RMPs. The general processes are again very similar for medicines and NAIMDs, but there are some differences that should be taken into consideration (see table 2):

Table 2. Risk Management processes for NAIMDs and medicines

	NAIMDs	Medicines
AE Coding	<ul style="list-style-type: none"> • Product problem: FDA and ISO • Patient Outcome: SNOMED, MedDRA, ICD, FDA 	<ul style="list-style-type: none"> • MedDRA
Signal Management Process	<ul style="list-style-type: none"> • Signal detection, signal validation, signal prioritization, signal escalation, regulatory actions and connections with other processes not as clearly regulated 	<ul style="list-style-type: none"> • Signal detection, signal validation, signal prioritization, signal escalation, regulatory actions clearly regulated
Benefit Risk Analysis	<ul style="list-style-type: none"> • Underdeveloped • RMF 	<ul style="list-style-type: none"> • PSURs/PBRERs • RMPs
Regulatory Actions	<ul style="list-style-type: none"> • Withdrawal, Recall, Restriction, Ban • DFU update, • Dear Doctor Letter (US), Field Safety Notice (EU) 	<ul style="list-style-type: none"> • Withdrawal • SmPC update, black box warning • Dear Doctor Letter

AERS Adverse Event Reporting System, AOANJRR Australian Orthopaedic Association National Joint Replacement Registry, CDER Center for Drug Evaluation and Research, EEA European Economic Area, EMA European Medicines Agency, EMR electronic medical records, ESID European Society of Immunodeficiencies, EUADR Exploring and Understanding Adverse Drug Reactions, EUREQUO European Registry of Quality Outcomes for Cataract and Refractive Surgery, FDA US Food and Drug Administration, MAUDE Manufacturer and User Facility Device Experience, MedSun Medical Product Safety Network, MHRA Medicines and Healthcare products Regulatory Agency, NAIMD non-active implantable medical devices, NorPD Norwegian Prescription Database, PAS post-authorization study, PASS post-authorization safety study, PRAC Pharmacovigilance Risk Assessment Committee, SCAAR Swedish Coronary Angiography and Angioplasty Registry, WHO World Health Organization

AE adverse event, DFU directions for use, FDA US Food and Drug Administration, ICD International Classification of Diseases, ISO International Organization for Standardiza-

tion, MedDRA Medical Dictionary for Regulatory Activities, PBRER periodic benefit–risk evaluation reports, PSUR periodic safety update reports, RMF risk management file, RMP risk management plan, SmPC Summary of Product Characteristics, SNOMED Systematized Nomenclature of Medicine

3.2.2.1. Adverse Event coding

Worldwide, the accepted adverse event coding for medicines is that of the Medical Dictionary for Regulatory Activities (MedDRA). This is the result of exhaustive work by many stakeholders and a comprehensive maintenance system by a private company (Maintenance and Support Services Organization (MSSO)) in charge of ensuring codes reflect changes and innovation (biologicals and other new products require constant additions to and refining of the dictionary).

The coding system for adverse events and product problems for NAIMDs is more heterogeneous than that for drugs. Different standardized nomenclatures exist for product problems (FDA codes and International Organization for Standardization (ISO) codes) and for patient outcomes (Systematized Nomenclature of Medicine-Clinical Terms (SNOMED CT), MedDRA, International Classification of Diseases (ICD), and FDA Patient Problem Codes). As seen in Table 3 (13–16), the standardized nomenclature systems vary significantly with regards to number of terms, granularity, hierarchy, and availability in different languages.

Table 3. Standardized Nomenclatures for Describing Patient Outcome

	MedDRA	SNOMED CT	ICD	FDA Patient Problem Codes
Number of terms	70,000	311,000	70,000	700
Hierarchy	High	Medium	Medium	Low
Number of languages available	11	5	42	1
Owner	International Conference on Harmonisation (ICH)	The International Health Terminology Standards	World Health Organization (WHO)	U.S. Food and Drug Administration (FDA)

ICD International Classification of Diseases, MedDRA Medical Dictionary for Regulatory Activities, SNOMED CT Systematized Nomenclature of Medicine Clinical Terms

3.2.2.2. Signal Management Process

The aim of signal detection for both medicines and NAIMDs is to promptly identify risks associated with the use of a product (17). Decisions as to whether a finding represents a ‘safety signal’ and whether it warrants further investigation can be challenging.

Quantitative signal detection is followed by a signal validation process that confirms whether or not the signal is real (Fig. 4). This is often verified through qualitative analysis of case evaluation. Thereafter, the signal is prioritized on the basis of the strength of the signal, whether or not the signal represents a new finding, the clinical importance and potential public health implications of the issue, and the potential for preventive measures to mitigate the adverse public health impact.

After signal prioritization, the manufacturer or marketing authorization holder decides whether or not the signal must be escalated and whether or not any regulatory actions should be taken as risk minimization measures to address the safety issue (17).

Although the signal management process is the same, the legislation requirements are better described in pharmaceutical regulations (18–20). This is not the case for NAIMDs; guidelines giving practical advice on signal management are yet to be developed. Drug regulations were developed earlier than medical device regulations, which explains and results in the poor description of legislation requirements for medical devices.

For medicines, new pharmacovigilance regulations in the EU have highlighted the relevance of signal management, and the European Medicines Agency’s recently established Pharmacovigilance Risk Assessment Committee (PRAC) has been instructed to supervise all aspects of the use of medicines, including signal management and prioritization (21). Numerous worldwide initiatives are investigating new methods to facilitate earlier signal detection, mainly through mining of routinely collected data from electronic healthcare records (EHRs) (22).

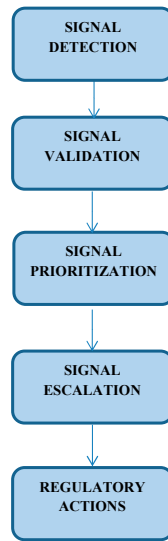


Figure 4. Signal management process for both non-active implantable medical devices (NAIMDs) and medicines

3.2.2.3. Post-market Benefit-Risk Analysis

Post-market benefit–risk analysis can be defined as a comparative assessment of benefits (positive effects) and risks (potential harms) of a particular product (medicinal product or medical device) after it has been introduced to the market. This is an iterative and dynamic process comprising four phases (Fig. 5). In the first stage, the benefits and risks should be defined. Thereafter, activities aimed at benefit optimization and risk mitigation or minimization should be outlined. During the third stage, the product should be assessed on the basis of its effectiveness and safety throughout its entire life cycle. In the fourth stage, the RMP should be

revised if the benefit–risk profile of the product has changed. The process is the same for both NAIMDs and medicines. However, the requirements for a benefit–risk analysis framework are more defined for medicines because of the more developed legislation. For medicines, there is a regulatory requirement to submit periodic safety update reports (PSURs)/periodic benefit–risk evaluation reports (PBRERs). PSURs/PBRERs are pharmacovigilance documents intended to provide an evaluation of the benefit–risk balance of a medicinal product. These reports are submitted by marketing authorization holders at defined time points during the post-authorization phase (23). PSURs/ PBRERs are not currently required for NAIMDs. In terms of risk-management document submission, there is a regulatory requirement for both medicines and NAIMDs: updated RMPs for medicines (24) and updated risk-management files (RMFs) for NAIMDs (25).

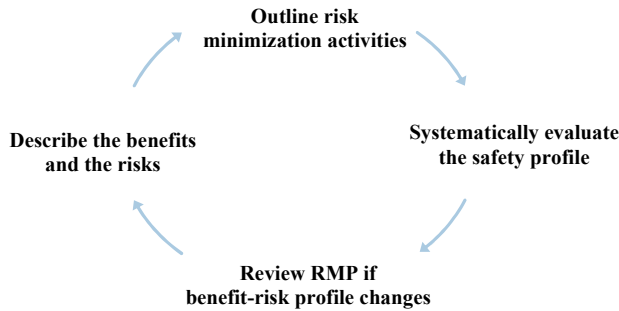


Figure 5. Post-market benefit-risk analysis for both non-active implantable medical devices (NAIMDs) and medicines
 RMP: Risk Management Plan

3.2.2.4. Regulatory Actions

Regulatory actions are well defined for both types of products. However, what constitutes a regulatory action differs, often by country or region, and there is no harmonization across jurisdictions. Moreover, the regulatory approval process for medical devices also differs widely across jurisdictions. For example, in the USA, the FDA approves the marketing of a new medical device and has tools to restrict the use of or ban a device and remove unsafe products from the market (17). Conversely, in Europe, the premarket evaluation of a device is performed by the notified body, which includes the assessment and verification of the clinical evaluation. Once medical devices bear the CE marking, they can circulate freely within the EU. In the post-market environment, it is sometimes difficult for the EU Member States to stop production, CE labelling, or distribution of medical devices (26). Medical devices marketed first in the EU have a higher risk of post-marketing safety issues than medical devices first marketed in the USA (27).

4. DISCUSSION

4.1. Role of the Patient

The patient needs to be aware of potential risks and able to easily communicate their personal experience relating to the safety and effectiveness of the device. Patient associations should be involved in defining the new regulations and guidelines for safety evaluation systems for medical devices.

Some initiatives have already been undertaken to try to develop a systematic methodology to calculate and include patient information into the medical device safety evaluation system (28) and encourage patient engagement (29). The goal should be to obtain a more patient-centric system. The patient should be a key stakeholder in public health.

4.2. Recommendations

The basic systems for safety evaluation of medical devices and medicines are not very different from a conceptual perspective; however, gaps currently exist in the safety evaluation of medical devices. This paper has identified these gaps, and some recommendations on how to fill these gaps follow. As seen in Fig. 6, the recommendations are ordered in three categories: harmonization and centralization, safety evaluation tools, and user training and customer service.

4.2.1. Harmonization and Centralization

Adverse event coding should be harmonized to improve the signal detection process. It is recommended that a global and centralized database, such as the World Health Organization (WHO) Vigibase, be established for the assembly of all medical device reports.

Moreover, a worldwide evaluation system should be developed for medical devices and should include representatives from the different stakeholders (12). This system also does not yet exist for medicines and could use real-world evidence to support regulatory decision making. To ensure successful implementation of this system, three steps need to be incorporated: (1) the UDIs need to be consistently assembled within electronic health information, (2) all stakeholders need to ensure a continual use of the EHRs, including UDIs, and lastly (3) to link patient data, all data sources need to have interoperable linking capabilities (30). This is a long-term goal because it involves policy change. Therefore, these three steps could take years or even decades.

For these harmonization and centralization recommendations to succeed, there must be active collaboration and support from all stakeholders.

Further to the recommendations listed above, there must be regulatory methodology harmonization: the regulatory approval process and the definitions of regulatory actions need to be aligned across jurisdictions to enable a more robust signal management process.

4.2.2. Safety Evaluation Tools

Post-market surveillance data are very important for medical devices because they provide valuable information regarding user variability. Relevant authorities could make more safety evaluation tools available to the different stakeholders to improve safety assessment:

1. Regulatory documents providing further guidance on the different steps in the signal management process. For instance, the following signal detection guidance has already been established for medicines: the report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group VIII and the guidelines on good pharmacovigilance practices (GVP) module IX—signal management (19, 20).
2. A post-market surveillance (PMS) plan should be submitted for every medical device or group of medical devices to serve as a summary of all collected post-market information and as a guide to utilizing such information (2).
3. A post-market clinical follow-up study plan should also be part of the PMS plan (2).
4. PSURs for every medical device or group of medical devices to reinforce the benefit–risk analysis process.
5. The clinical data required (from both a quantitative and a qualitative perspective) to obtain the market approval should be defined in guidelines and should be consistent with the risk associated with the product and/or how innovative the device is. Medical devices with a high level of innovation (new material, new product, new surgical procedure) and/or a high level of risk should require more clinical data. For these types of products, more evidence should be generated during the premarket phase to better define expected risks. Single-blind randomized controlled trials (RCTs) with these types of implantable medical devices should be conducted when required and if possible. Previous experience with similar devices should also be considered as evidence when deciding the clinical data required.

4.2.3. User training and customer service

As previously (Fig. 1), user error and the user’s learning curve are two vital factors contributing to adverse events with medical devices. Manufacturers should primarily focus on user training as the most important risk minimization tool. Proper training should be provided to reduce user variability. Providing excellent customer service to the medical device user will supply the manufacturer with substantial knowledge about the medical device safety profile. To guarantee outstanding customer service, training standards need to be implemented to ensure consistent quality. Moreover, all involved staff members need to be trained on these standards and briefed about the company’s vision on customer service. To measure the efforts of staff and to evaluate the success of the training, a framework should be designed to measure quality and its

consistency. Lastly, the company can only learn and grow from opinions and feedback from their customers. This should be received through customer surveys, which should be shared with the team and made public to all stakeholders (12).

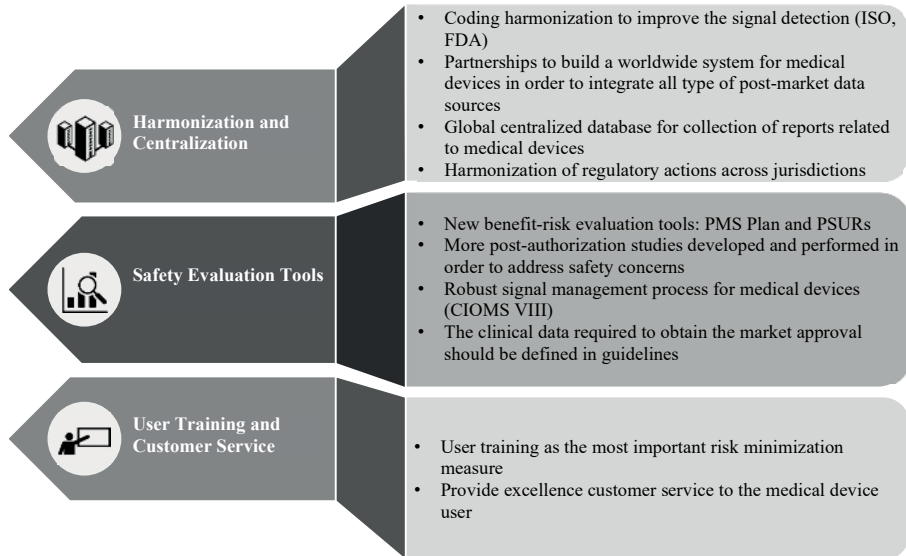


Figure 6. Recommendations to cover the gaps in the safety evaluation of medical devices

CIOMS Council for International Organizations of Medical Sciences, FDA US Food and Drug Administration, ISO International Organization for Standardization, PMS post-market surveillance, PSUR periodic safety update reports

5. CONCLUSIONS

Traditionally, the collection of safety information and its integration into the risk management process of medical devices has been neither consistent nor performed for all products.

To address this weakness, health authorities have started to work on new regulatory documents. Patients must be the key pillars and public health the cornerstone of this new system. Now is the time for collaboration between all stakeholders to develop a more proactive safety evaluation process. This new process should incorporate real-world data to develop a risk assessment model that is suitable for all medical devices.

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CONFLICT OF INTEREST

Josep Pane and Irene Rebollo are employees of Alcon, Novartis which manufactures NAIMDs. Preciosa Coloma, Katia Verhamme and Miriam Sturkenboom have no conflicts of interest that are directly relevant to the content of this study.

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CHAPTER 3

CASE STUDY – DESCRIPTIVE ANALYSIS OF SAFETY SURVEILLANCE DATA

3.1

Descriptive analysis of Post-market Surveillance data for hip implants

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Keywords: medical devices, spontaneous reports, complaint data collection, post-market surveillance, complaint data analysis

ABSTRACT

Background

Recent safety issues involving medical devices have highlighted the need for better post-market surveillance (PMS) evaluation. This article aims to describe and to assess the quality of the PMS data for a medical device, and finally to provide recommendations to improve the data gathering process.

Methods

Descriptive analysis of Medical Device Reports (MDRs) on the use of MRA, a specific type of hip implant replacement submitted to the Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database from 01-Jan-2008 to 31-Dec-2017. The number of reports was described as the number of MDRs per unique MDR number and stratified by different variables.

Results

The total number of reports related to MRA was 2,377 and the number of MDRs per year ranged between 84 in 2009 and 452 in 2017. Most of the reports were reported by manufacturer Depuy Johnson & Johnson and were reported by a physician. In 44.9% of the reports, the device problem was reported as “Unknown”. If the device problem was known, in the majority of cases, it was related to an implant fracture.

Discussion

The underlying data should meet high-quality standards to generate more evidence, and to ensure a timely signal generation. This case study shows that the completeness and quality of the MDRs can be improved. The authors propose the development of tools to ensure a more dynamic complaint data collection to contribute to this enhancement.

Key Points

- The completeness and the quality of the data included in the medical device reports can be improved.
- New standards and safety tools should be developed to ensure a more dynamic complaint data collection process.

1. INTRODUCTION

An implantable medical device is a device that is partly or totally inserted into the human body or a natural orifice or is used to replace the surface of the body and is expected to stay in use for 30 days or more. Examples of implantable medical devices include dental implants, breast implants, hip implants and intraocular lenses. Surgical or medical procedures are used to insert, apply and remove implantable medical devices. To be classified as a non-active implantable medical device (NAIMD), the medical device should not have an integral power source; all devices with a power source are considered active implantable medical devices (eg, pacemaker, cochlear implants...) (1).

Recent safety issues involving NAIMD have highlighted the need for better premarketing and post-marketing evaluation (2,3). In the metal-on-metal (MoM) hip safety issue, thousands of patients around the world may have been exposed to high levels of toxic metals from failing hip implants. The chromium and cobalt ions from the MoM hip implants could enter into the tissues of patients with this type of hip implants, leading to reactions that damaged the muscle and bone, and led to revision procedures or left some patients with long-term disability (4-7). This safety issue was only identified by the Australian Health Authorities upon review of the Australian Orthopaedic Association National Joint Replacement Registry, and this finding was confirmed by the National Joint Replacement Registry of England, Wales, and Northern Ireland and the New Zealand Registry. This resulted in a worldwide recall of the MoM hip implants. The safety issue was highly publicized as MoM hip implants were approved for market use although lacking data derived from clinical trials. In addition, the manufacturers did not effectively review post-market clinical data (including device registries containing post-market surveillance information) and thus failed to identify and report this risk to the health authorities (8).

A prior safety issue with Poly Implant Prosthesis breast implant scandal (3) had also contributed to the emerging growing demand to improve the current passive-reactive post-market surveillance (PMS) system of medical devices. An important part of this PMS system is the data collection of case (complaint) reports. To enhance the current surveillance system, it is important to measure and assess the quantity and quality of PMS data on medical devices.

Hip implants are NAIMD that are implanted during hip replacement surgery. Hip replacement surgery can be performed traditionally or by means of a minimally invasive technique. The main difference between the two procedures is the size of the incision and the type of prosthetic implant, either a total hip replacement or a MoM hip replacement (9). With approximately 1.4 million hip implant surgeries performed every year around the world, it is the

most common joint replacement procedure. In the United States, over 231,000 surgeries are performed annually (10).

Given the large use of hip implants and the need to improve medical device vigilance, we performed a case study and conducted a descriptive analysis of the PMS data from one of the most important publicly available spontaneous reports database (11), the Food and Drug Administration's (FDA) Manufacturer and User Facility Device Experience (MAUDE) database, to assess the quality and the quantity of these spontaneous reports using hip implants as a proof of concept, but our aim was not to investigate and compare the safety of individual (or specific) implants.

2. METHODS

2.1. Data Source

The PMS data for hip implants were extracted from the FDA MAUDE database. Medical device reports (MDRs) on the use of hip implant replacement were extracted from the FDA MAUDE of MDRs received by the FDA between 1 January 2008 and 31 December 2017. MAUDE contains MDRs received by the FDA on worldwide complaint data. Adverse events or technical complaint information of medical devices can be reported to the FDA via user facility (hospital), consumer or manufacturer.

Manufacturers must submit MDRs to the FDA “when they become aware of information that reasonably suggests that one of their marketed devices may have caused or contributed to a death or serious injury or has malfunctioned and the malfunction of the device or a similar device that they market would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. Manufacturers must send MDRs of such deaths, serious injuries and malfunctions to the FDA” (12) when they become aware of any of the events described above reported from any country in the world. The definition of serious injury is described below.

The FDA provides access to MAUDE information through three different tools: (a) an on-line simple (single-parameter) interface, (b) advanced (multiparameter) search interface or (c) downloadable data files. These online search engines are extremely convenient; however, information obtained using these interfaces has some restrictions (12-14). In our study, we used both the online search interface and the downloadable datasets.

2.2. Outcomes

For this study, we were interested in reports related to the use of another type of hip implant (different from the MoM implant): the hip joint metal/ceramic/ceramic/metal semi-constrained cemented or uncemented prosthesis (FDA product code: MRA) (15). We considered all events related to this type of device as events of interest. The FDA has a standardized vocabulary for adverse events and product problems. A total of 167 different event codes related to the use of the hip implant of interest (MRA) were analyzed. Malfunctions and serious injuries were classified according to the FDA regulatory definitions (16); a serious injury is an injury or illness that is life-threatening, results in permanent impairment/damage or necessitates medical/surgical intervention to preclude permanent impairment/damage. A malfunction stands for the failure of a device to meet its performance specifications or to perform as intended (Performance specifications include all claims made in the labeling of the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed (16).

The type of reporter was classified as unknown or known (physician, nurse, patient, pharmacist, administrative and known others). The type of reported adverse events was classified as malfunction and/or serious injury (for definitions, see above). The complaint sample availability and the corrective/remedial actions field were classified as Yes, No or NA.

2.3. Data management and analysis

The study period comprised 10 years, and data for this period (1 January 2008 through 31 December 2017) were obtained from three MAUDE downloadable datasets: the MDR Freedom of Information (FOI) master dataset, the Device Data dataset and the FOI Device Problem dataset. The advanced search interface dataset was used to obtain the name of all MRA hip implant manufacturers (filtering by date on which the report was received by the FDA (1 January 2008 through 31 December 2017) and product code MRA) with reported MDRs. The advanced search interface dataset was used to obtain the name of all MRA hip implant manufacturers. We had to standardize the manufacturer names by classifying each of the names from the manufacturer's column into eight different categories: Depuy Johnson & Johnson, Stryker, Wright Medical Technology, Zimmer, Encore, Stelkast, Exactech and Smith & Nephew.

We obtained the following information from each of the downloadable datasets:

- The MDR FOI Master dataset, filtering by the “manufacturer name” field for all the MRA Hip Implant Manufacturers available. The following variables were used: MDR report key, manufacturer name, type of event, report source, source type (country of origin; United States or foreign), reporter occupation, remedial actions and recalls.

- The Device Data dataset, filtering by “MDR report key.” The following variables were used from this dataset: MDR report key number (to link), device availability and device evaluated by the manufacturer.
- The FOI Device Problem dataset, filtering by “MDR report key.” The following information was used from this dataset: MDR report key Device Problem codes.

From these three datasets, one unique dataset was built using the “MDR report key,” which was available in the three downloadable datasets.

The data were analyzed using descriptive statistics, reporting counts, proportions and stratifications. Absolute numbers and percentages were described by manufacturer, brand name, type of event (death, injury, malfunction, NA, other), reporter’s occupation, type of reported adverse events and product problems, complaint sample availability (whether the device is available for further investigation) and corrective/remedial actions. The numerator was the number of reports with MRA hip implants for a specific brand name, and the denominator was the total number of reports for MRA hip implants during the study period.

3. RESULTS

Eight MRA hip implant manufacturers reported MDRs to the FDA: Depuy Johnson & Johnson, Stryker, Wright Medical Technology, Zimmer, Encore, Stelkast, Exactech and Smith & Nephew. A total of 2377 unique FDA-reportable complaints for MRA hip implants were received by the FDA from the manufacturer between 1 January 2008 and 31 December 2017, mostly originating in the United States (1807 reports, 76.0%). There was a high percentage of missing information. The proportion of reports with information on the type of device problem was 55.1% (in 44.9% of the reports, the device problem was reported as “Unknown”). The most frequently reported device problems included “implant fracture” (39.57%, 518 reports), “dislocation” (11.38%, 149 reports), “loss of osseointegration” (8.40%, 110 reports), “component/fitting issue” (2.60%, 34 reports), “material corrosion” (1.91%, 25 reports) and “metal shedding debris” (0.61%, 8 reports) (Table 1).

Compared to all other MRA hip implant manufacturers, Depuy Johnson & Johnson had the most MDRs (64.28%, 1528 reports). For the other manufacturers, the number of reports for MRA hip implants were as follows: Stryker (22.97%, 546 reports), Wright Medical Tech (8.08%, 192 reports), Smith & Nephew (1.94%, 46 reports), Zimmer (1.77%, 42 reports), Exactech (0.51%, 12 reports), Encore Medical (0.34%, 8 reports) and Stelkast (0.13%, 3 reports). Death occurred in 0.08% (2 reports), and serious injury occurred in 72.11% (1714 reports) (Table 1). The number of yearly MDRs increased from 84 in 2009 to 452 in 2017 (Figure 1).

Table 1. Overview of the characteristics of medical device reporting (MDR) data reported between 01-Jan-2008 through 31-Dec-2017

Manufacturer	Number of MDRs (% of total)
Depuy Johnson & Johnson	1,528 (64.28)
Stryker	546 (22.97)
Wright Medical Tech	192 (8.08)
Smith & Nephew	46 (1.94)
Zimmer	42 (1.77)
Exactech	12 (0.51)
Encore Medical	8 (0.34)
Stelkast	3 (0.13)
Device Problem	
Known	1,309 (55.07)
Unknown	1,068 (44.93)
Known Device Problem	N=1309
Fracture/Break/Crack/Scratched material	518 (39.57)
Dislodged/Dislocated/Displaced/ Disassembly/Malposition/Migration or expulsion of device	149 (11.38)
Loss of Osseointegration/Failure to Bond	110 (8.40)
Component Issue/Connection Issue/Implant Loose Fitting issues/Inadequacy of Device Shape/Size/	34 (2.60)
Material Corrosion/Degradation/ Integrity/Deformation/Naturally Worn	25 (1.91)
Metal Shedding Debris	8 (0.61)
Other	465 (35.52)
Type of event	
Death	2 (0.08)
Serious Injury	1,714 (72.11)
Malfunction (no serious injury)	653 (27.47)
Other	4 (0.17)
Unknown	4 (0.17)
Country of origin	
US	1,807 (76.02)
Foreign (Rest of the World excluding US)	514 (21.62)
Unknown	56 (2.36)
Report Source Code	
Manufacturer	2,377
User facility	0
Distributor	0
Voluntary	0

Table 1. Overview of the characteristics of medical device reporting (MDR) data reported between 01-Jan-2008 through 31-Dec-2017 (*continued*)

Manufacturer	Number of MDRs (% of total)
Reporter Occupation	
Physician	913 (38.41)
Health Professional other than physician	445 (18.72)
Attorney	89 (3.74)
Patient	28 (1.18)
Risk Manager	14 (0.59)
Pharmacist	7 (0.30)
Company Technician/Representative	7 (0.30)
Others	752 (31.64)
Unknown	122 (5.13)
YES	627 (26.38)
NO	1,716(77.19)
Unknown	34 (1.43)
Device Availability	
YES	627 (26.38)
NO	1,716(72.19)
Unknown	34 (1.43)
Device Evaluated by Manufacturer* out of the available devices	
YES	423 (67.46)
NO	88 (14.04)
Unknown	116 (18.50)
Remedial Action	
Other	630 (26.50)
Recall	3 (0.13)
Modification/adjustment	1 (0.04)
BLANK	1,743 (73.33)
Recalls – Removal Correction Number	
Z-1749/1816-2011 (Depuy Johnson & Johnson)	2 (66.67)
BLANK (Depuy Johnson & Johnson)	1 (33.33)
TOTAL	3

*Note: the device can only be evaluated by the manufacturer if it is available.

The reporter's occupation was reported in 94.9% of all reports, of which 40.5% of reporters were physicians (Table 1); 100% of the reports were submitted by the manufacturer, and no reports were submitted directly to the FDA by physicians, nurses, other healthcare providers or patients.

The proportion of reports with information on the suspect device availability was higher (98.57%, 2343 reports), and the device was only available in 26.38% of the reports (627 reports). The manufacturer was only able to evaluate the suspect sample in 17.80% of the reports (423 reports). Without a sample, it is more difficult to identify the root cause of the event and take appropriate actions. A remedial action was only identified for 26.67% (634 reports) of the reports, and only 0.47% (3 reports) of the remedial actions were associated with a recall. The three reports associated with a recall came from the same manufacturer, namely, DePuy Johnson & Johnson (Table 1).

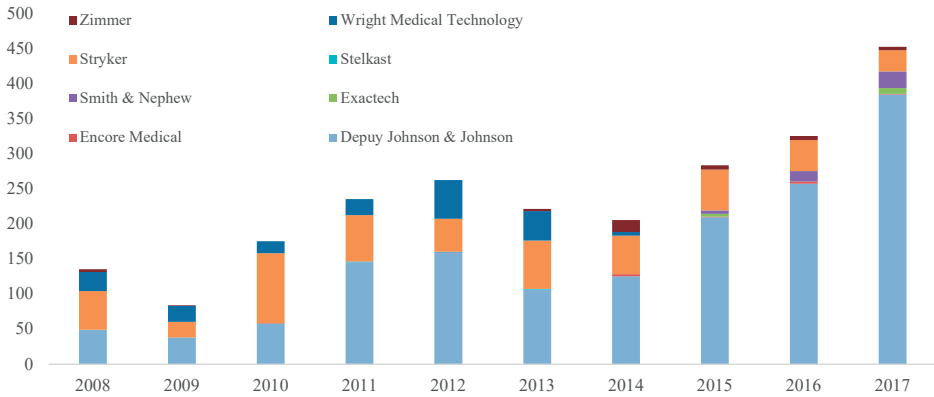


Figure 1. Number of medical device reports related to MRA hip implant by manufacturer per year from 01-Jan-2008 through 31-Dec-2017

4. DISCUSSION

This case study on medical device reporting on MRA hip implants to the FDA demonstrated some key findings. First, beyond the United States, very few reports were received from other countries, and no reports were submitted by physicians, nurses, other healthcare providers or patients. Second, most reports were on serious injury, and the most frequently reported device problem was “fracture of the hip implant.” Third, completeness of information in the reports was poor, and often, the suspect sample was not sent to the manufacturer and therefore could not be evaluated, which hampers the root cause analysis.

These results underline the need to obtain better post-market complaint data for medical devices within the United States and beyond (Figure 2). Improvements can be made in the reporting itself, the collecting database and the awareness of the different stakeholders involved in the safety evaluation process. High quality standards with a consistent and structured approach are needed to optimally gather MDR. More specificity in regulatory reporting and

harmonized regulatory coding might help to generate better evidence to ensure an accurate and well-timed signal generation.

To address this problem of quality issues in reporting, as well as in the completeness of data, the manufacturer and the health authorities should engage the reporter (patient or healthcare professional) in the complaint data collection process. In addition, the regulators and the manufacturers could provide tools to healthcare providers and users that would give more guidance on complaint reporting and appropriate coding. Examples of such tools could be the development of educational material for the healthcare professionals about complaint reporting, including a list of key fields to be completed by the reporter; guidance providing instructions on how to manipulate complaint samples that have been in contact with human fluids and how to return them to the manufacturer, ensuring safe transport to maintain the integrity of the complaint sample; the regulatory coding harmonization and global implementation across jurisdictions; and coding guidelines developed by the regulators for each type of medical device and provided to all the stakeholders.

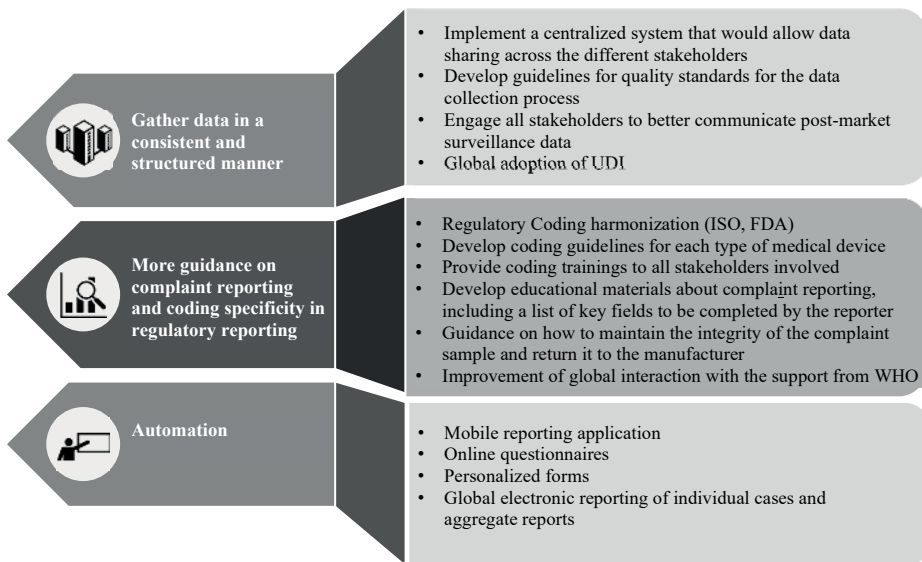


Figure 2. Recommendations to obtain better post-market complaint data for medical devices

Abbreviations: FDA, Food and Drug Administration; IMDRF, International Medical Device Regulators Forum; ISO, International Organization for Standardization; UDI, Unique Device Identifier; WHO, World Health Organization

To stimulate reporting and facilitate timely reporting, the process should be automated, and healthcare professionals could be involved in the use of digital reporting tools such as

Table 2. Recommendations to improve MDR reporting and the MAUDE database

	Limitation	Recommendations	Owner
Event coding	<ul style="list-style-type: none"> Impossibility to identify patient harms and root causes associated with specific FDA device problem codes. 	<ul style="list-style-type: none"> FDA Patient codes and FDA investigational codes (methods, results and conclusions) publicly available in MAUDE. 	<ul style="list-style-type: none"> FDA
Patient exposure	<ul style="list-style-type: none"> Lack of information about frequency of device use does not allow to estimate patient exposure. 	<ul style="list-style-type: none"> The manufacturers could make their distribution/sales data available to the Health Authorities, upon request. 	<ul style="list-style-type: none"> Global Health Authorities (including FDA), Manufacturers
Root cause identification	<ul style="list-style-type: none"> For the majority of reports the suspect sample is not available and cannot be evaluated by the manufacturer. Identifying the root cause of the event is especially difficult if the device in question has not been identified and directly evaluated by the manufacturer. The MAUDE advanced search interface is updated monthly and the search page reveals the date of the latest update. The FDA pursues to include all reports received before the update but the inclusion of some reports may be delayed. 	<ul style="list-style-type: none"> Global adoption of Unique Device Identifier: in order to identify the device and link the device to a Serial Number, UDI needs to be present on the device, and readily accessible in the medical record. More guidance and training to the healthcare professionals on the importance of sending the device with all the adequate information (including UDI) to the manufacturer for evaluation, if the suspect device is explained. 	<ul style="list-style-type: none"> Reporting facilities, FDA, Manufacturers
Timely reporting	<ul style="list-style-type: none"> More guidance and training on the importance of timely reporting should be provided to the different stakeholders involved in the complaint handling process 	<ul style="list-style-type: none"> More guidance and training on the importance of timely reporting should be provided to the different stakeholders involved in the complaint handling process 	<ul style="list-style-type: none"> Reporting facilities
Report source	<ul style="list-style-type: none"> Most of the MDRs from MAUDE come from spontaneous reports received from the manufacturer. This type of reports may be associated with reporting bias. 	<ul style="list-style-type: none"> Healthcare provider reports directly to the FDA needs to be strongly encouraged via training and regulatory guidelines. Enriching the FDA MAUDE PMS data with data from medical device registries. In order to be able to link the registry data with the manufacturer reports data common standardized data set including UDI should be created. 	<ul style="list-style-type: none"> FDA

Table 2. Recommendations to improve MDR reporting and the MAUDE database (*continued*)

	Limitation	Recommendations	Owner
Scope	<ul style="list-style-type: none"> • MAUDE only includes FDA reportable complaints. If the complaint does not meet the FDA reporting criteria, the complaint will not be in MAUDE. • MAUDE only includes complaints associated with medical devices that are marketed in the US. If the medical device is not marketed in the US, the complaint will not be in MAUDE. 	<ul style="list-style-type: none"> • Exchange of PMS data (including FDA non-reportable complaints and trend reports for FDA non-reportable complaints) between different Health Authorities. • Development of a global repository to store global PMS data for medical devices. 	<ul style="list-style-type: none"> • IMDRE, Global Health Authorities (including FDA)

Abbreviations: FDA, Food and Drug Administration; PMS, Post-market Surveillance; UDI, Unique Device Identifier

mobile applications, online questionnaires, personalized forms and global electronic reporting of individual cases and aggregate reports, which can lead to quality improvement of the collected information (17). Table 2 provides recommendations not only on how to improve MDR reporting but also recommendations on how to improve data collection in the MAUDE database.

In addition to the limitations described in Table 2, our results also have additional limitations as post-marketing complaint data is prone to reporting bias (18). Moreover, a descriptive analysis of post-marketing complaint data does not allow to control patient predisposing factors such as family history, health condition or previous surgeries. Therefore, we recommend enriching the FDA MAUDE data with PMS data from medical device registries. To link the registry data with the spontaneous report data from MAUDE, a common Unique Device Identifier (UDI) should be created. The UDI enables the unequivocal identification of the medical device by providing a single global identifier that can be used to link and integrate the existing FDA MAUDE database with medical device registries (19). The global use of a UDI facilitates traceability throughout distribution and allows the recording of medical devices used in patients. The UDI makes it possible to link patient, device and adverse event/product problem and/or related data repositories.

This information can help the different stakeholders involved in the safety evaluation of medical devices to quickly gather and evaluate spontaneous reports or data from registries and act accordingly.

To improve the ability to signal problems on a global scale, a global harmonization and repository/database (similar to the World Health Organization (WHO) Vigibase for medicinal products) should be created to allow sharing of information across the different stakeholders (health authorities, users, manufacturers, notified bodies and health professionals) in addition to the development of quality standards for the data gathering and a global centralized database to collect and store reports related to medical devices. To ensure success, regulators should partner with the manufacturers, which could be facilitated by the improvement of worldwide interactions between different stakeholders with support from the WHO, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), Council for International Organizations of Medical Sciences (CIOMS) and the International Medical Device Regulators Forum (IMDRF). WHO, ICH and CIOMS should provide their experience and lessons learned from the global harmonization of medicinal products, and IMDRF should play a significant role in the standardization of quality standards across the different regulatory bodies (20).

In conclusion, there is an urgent need for better PMS for medical devices, which we demonstrate through the MRA hip implant example. The quality of post-market complaint data

and their timely collection are crucial for the validity of the complaint reports. It is time to face current challenges such as the lack of quality standards, lack of specificity in regulatory reporting, lack of harmonized coding and lack of engagement from reporters at the time to send samples back for analysis. We recommend that the different stakeholders in this process (manufacturers, health authorities, healthcare professionals and patients) work together to overcome these challenges.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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CHAPTER 4

**SAFETY SIGNAL DETECTION AS A KEY
PROCESS FOR EFFECTIVE SAFETY
SURVEILLANCE OF MEDICAL DEVICES**

4.1

Challenges associated with the safety signal detection process for medical devices

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coding dictionaries, medical devices

ABSTRACT

Background: Previous safety issues involving medical devices have stressed the need for better safety signal detection. Various European Union (EU) national competent authorities have started to focus on strengthening the analysis of vigilance data. Consequently, article 90 of the new EU regulation states that the European Commission shall put in place systems and processes to actively monitor medical device safety signals.

Methods: A systematic literature review was conducted to synthesize the current state of knowledge and investigate the present tools used for medical device safety signal detection. An electronic literature search was performed in Embase, Medline, Cochrane, Web of science, and Google scholar from inception until January 2017. Articles that included terms related to medical devices and terms associated with safety were selected. A further selection was based on the abstract review. A full review of the remaining articles was conducted to decide on which articles finally to consider relevant for this review. Completeness was assessed based on the content of the articles.

Results: Our search resulted in a total of 20,819 articles, of which 24 met the inclusion criteria and were subject to data extraction and completeness scoring. A wide range of data sources, especially spontaneous reporting systems and registries, used for the detection and assessment of product problems and patient harms associated with the use of medical devices, were studied. Coding is remarkably heterogeneous, no agreement on the preferred methods for signal detection exists, and no gold standard for signal detection has been established thus far.

Conclusion: Data source harmonization, the development of gold standard signal detection methodologies and the standardization of coding dictionaries are amongst the recommendations to support the implementation of a new proactive approach to signal detection. The new safety surveillance system will be able to use real-world evidence to support regulatory decision-making across all jurisdictions.

1. INTRODUCTION

Signal detection is defined by the International Medical Device Regulators Forum (IMDRF) as “The process of determining patterns of association or unexpected occurrences that have the potential to impact patient management decisions and/or alter the known benefit-risk profile of a device (1)”. The aim of safety signal detection for medical devices is to promptly identify risks associated with the use of a product (2). Signals can be production related (e.g., a defective batch or a released series of batches) or linked to the design and/or use. Signals can be identified during the pre-market surveillance phase using clinical trial data, or during the post-market surveillance phase using post-market data sources. The decision of whether a finding represents a “signal” and whether such finding is subject to further investigation can be challenging. For medicinal products, quantitative safety signal detection is followed by a signal validation process during which the signal is verified to be real or not. This process is often performed through careful case evaluation. Thereafter, signal prioritization is completed depending on the strength of the signal, whether or not the signal represents a new finding, the clinical importance and potential public health implications, and the availability of preventive measures to mitigate the adverse public health impact (3). After prioritization, the marketing authorization holder together with the regulators has to decide whether additional risk minimization measures are needed to address this safety issue (2). Although the signal management for medicinal products and medical devices are conceptually equivalent, the legislation requirements are better described in the pharmaceutical regulation (4–6) than in the medical devices regulations. For the latter, the guidelines defining requirements and giving practical advice on signal management are yet to be developed. Recent safety issues involving medical devices have highlighted the need to improve signal detection (7). Various European Union (EU) national competent authorities have started to focus on strengthening the analysis of vigilance data of medical devices. As a consequence, the new EU medical device regulation was published; namely, article 90 that states that the European Commission shall put in place systems and processes to actively monitor the data available in order to identify trends, patterns or signals that may reveal new risks or safety concerns (8). In this paper, we aim 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.

2. METHODS

We performed a systematic literature review to identify articles describing different aspects associated with safety signal detection for medical devices (see Table 1).

Table 1. Systematic Literature Review Methodology

Step	Inclusion Criteria	Exclusion Criteria	Number of Articles
Electronic Search	<ul style="list-style-type: none"> Embase, Medline, Cochrane, Web of science, and Google scholar using terms that included “medical device” and terms attributable to safety (“signal detection” or “post-marketing surveillance” or “risk management”). 	<ul style="list-style-type: none"> Articles that did not include “medical device” or terms attributable to safety (“signal detection” or “post-marketing surveillance” or “risk management”). 	<ul style="list-style-type: none"> 20,819
Restrictive Query Search	<ul style="list-style-type: none"> Any abstracts from the list of selected articles (20,819) with years ranging 2004-2017 (Jan-2004 through Jan-2017) and containing any of the following terms: “Signal” OR “Adverse reaction” OR “Adverse event” OR “Injury” OR “Malfunction” OR “Product problem”. 	<ul style="list-style-type: none"> Any abstracts from the list of selected articles (20,819) that did not include any of the following terms: “Signal” OR “Adverse reaction” OR “Adverse event” OR “Injury” OR “Malfunction” OR “Product problem”. 	<ul style="list-style-type: none"> 996
Abstract Review	<ul style="list-style-type: none"> Articles were included if the abstract review (996) contained any the following items: “post-market safety data sources in medical devices” OR “signal detection methodologies for medical devices” OR “medical device event coding dictionaries”. 	<ul style="list-style-type: none"> Articles were excluded if the abstract review (996) did not include any of the following items: “post-market safety data sources in medical devices” OR “signal detection methodologies for medical devices” OR “medical device event coding dictionaries”. 	<ul style="list-style-type: none"> 45
Full-Text Review	<ul style="list-style-type: none"> Articles (45) were reviewed and selected if the article included any information related to “medical device Post-Market Surveillance (PMS) data sources” OR “Methodologies used for signal detection for medical devices” OR “Coding dictionaries for medical devices”. 	<ul style="list-style-type: none"> Articles (45) were excluded if the article did not include any information related to “medical device Post-Market Surveillance (PMS) data sources” OR “Methodologies used for signal detection for medical devices” OR “Coding dictionaries for medical devices”. 	<ul style="list-style-type: none"> 24

We searched Embase, Medline, Cochrane, Web of science, and Google scholar using terms that included “medical device” and terms attributable to safety (“signal detection” or “post-marketing surveillance” or “risk management”), following Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for systematic reviews. Appendix A outlines the strings that have been used. Due to the high number of articles that resulted from the initial search, we decided to implement a restrictive query search on the abstracts from the list of selected articles in order to narrow down the selection. This restrictive query consisted of: any abstract with date range year 2004–2017 (Jan-2004 through Jan-2017) containing any of the following terms: “Signal” OR “Adverse reaction” OR “Adverse event” OR “Injury” OR “Malfunction” OR “Product Problem”.

2.1. Review of Articles

Following the query, all remaining abstracts were reviewed. Articles were excluded if the abstract review did not include any of the following items: “post-market safety data sources

in medical devices”, “signal detection methodologies for medical devices” or “medical device event coding dictionaries”. Articles containing the latter terms were included in the further study. Subsequently, a full-text review was conducted for each of the remaining articles. Articles were excluded if they did not include any information related to “medical device Post-Market Surveillance (PMS) data sources” OR “Methodologies used for signal detection for medical devices” OR “Coding dictionaries for medical devices”. All remaining full-text articles were subject to a formal evaluation to extract information on the following items (articles that did not contain at least one of the following items were excluded):

1. Type of PMS data sources on medical devices:
 - Spontaneous reporting systems (SRS) are reactive systems that contain reports on patient harms and product problems collected from healthcare professionals, patients, healthcare authorities and manufacturers whether reported directly or through published articles.
 - A medical device registry is defined by the IMDRF as an “Organized system with as primary aim to increase the knowledge on medical devices contributing to improve the quality of patient care that continuously collects relevant data, evaluates meaningful outcomes and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale. (eg international, national, regional, and health system)”(1)
2. Methodologies used for signal detection for medical devices.
3. Coding dictionaries for medical devices.

Each article was scored 1, 2 or 3 points depending on its content. The total score represents the sum of all three topics; 1 point being attributed to articles containing one of the three topics, 2 points being attributed to articles containing two of three topics, and finally, 3 points being attributed to articles containing all three topics. This score serves as a measure of the articles’ completeness. Following the author’s full-text review, KV conducted a second review of the full-text articles. KV agreed with the initial selection of the 24 articles, and the assigned score based on the described inclusion and exclusion criteria.

3. RESULTS

Our initial search strategy identified a total of 20,819 articles (10,199 Embase, 8,374 Medline Ovid, 1,501 Web of Science, 545 Cochrane and 200 Google Scholar). After applying specific search restrictions, a total of 996 abstracts were identified. During the abstract review, 951 articles were excluded, due to lack of information on any of the three key contents: post-market data sources for medical devices, signal detection methodologies for medical devices and coding dictionaries for medical devices. A total of 45 articles were included for full-text review.

During the review cycle, 21 articles were excluded due to the lack of information on any of the three key topics. Details of the 24 remaining articles are shown in Table 2.

Papers were categorized into two different categories: 11 review articles, and 13 studies (12 retrospective studies and 1 prospective study). Completeness scoring yielded 13 articles with a score of 1, 11 with a 2 point score, whereas no article scored a 3 point rating. 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 (Figure 1).

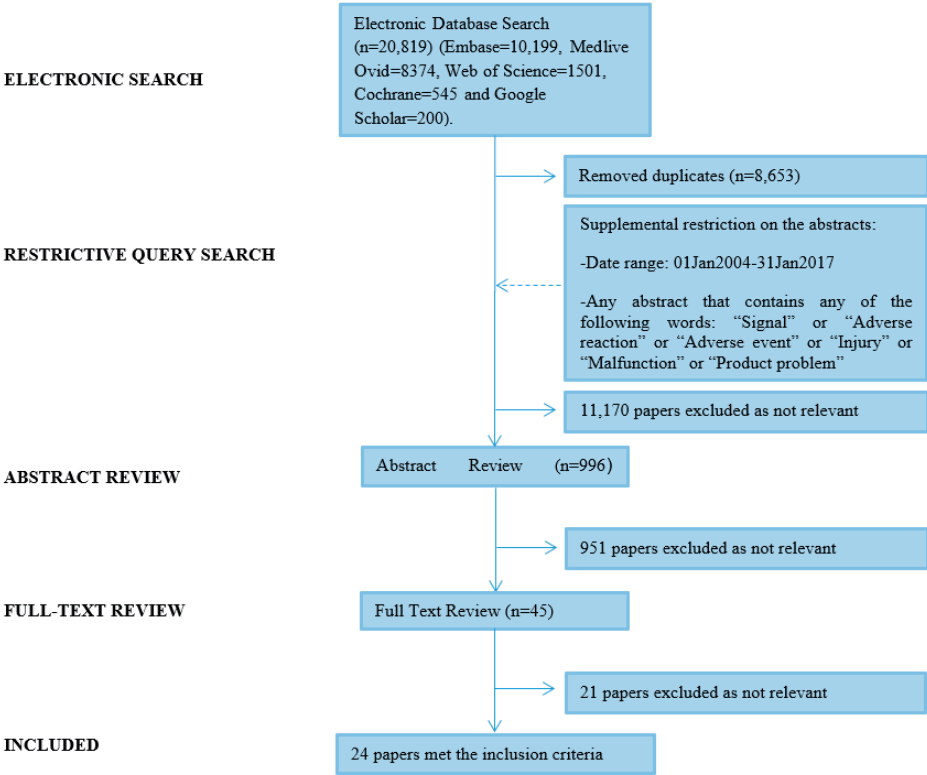


Figure 1. PRISMA flow diagram outlining all steps for the inclusion of articles in the review.

Table 2. Characteristics of the 24 Selected Articles

Title of Article	Type of Article	Authors	Journal	Year of Publication	Study Period	Number of Participants or Number of Reports	Post-Market Data Sources Medical Devices	Signal Detection Methodology for Medical Devices	Coding Dictionary for Medical Devices	Completeness Score
Adverse event Triggered Event Reporting for Devices: Report of a Food and Drug administration-supported feasibility pilot of automated adverse event reporting	Review article, feasibility study	Reed, T. L., Levy, D., Steen, L. T., Roach, J., Taylor, T., Call, K., Marion, J., Drozda, J. P.	J Clin Eng	2016	NA	NA	Yes, Adverse Event Triggered Reporting for Devices (ASTER-D)	No	No	1
An analysis of implantable cardiac device reliability. The case for improved post-marketing risk assessment and surveillance	Retrospective study	Laskey, W., Awad, K., Lum, J., Skodacek, K., Zimmerman, B., Selzman, K., Zuckerman, B.	Am J Ther	2012	January 2003-December 2007	256,392 CRT-D=> 1,925 malfunctioning; 459,000 ICD=> 10,593 malfunctioning	Yes, FDA annual reports (ICDs and CRT-D implants)	No	No	1
An evaluation of a distributed medical device safety surveillance system: The DELTA network study	Multicenter prospective study	Vidi, V. D., Matheny, M. E., Donnelly, S., Resnic, F. S.	Contemp Clin Trials	2011	January 2010 - December 2011	not specified but this is a paper discussing a study that still needs to be performed	Yes, American College of Cardiology's National Cardiovascular Registry (ACC-NCDR)	Yes, DELTA	No	2

Title of Article	Type of Article	Authors	Journal	Year of Publication	Study Period	Number of Participants or Number of Reports	Post-Market Data Sources Medical Devices	Signal Detection Methodology for Medical Devices	Coding Dictionary for Medical Devices	Completeness Score
Analysis of the US Food and Drug Administration Manufacturer and User Facility Device Experience database for adverse events involving Amplatzer septal occluder devices and comparison with the Society of Thoracic Surgery congenital cardiac surgery database	Retrospective study	DiBardino, D. J. McElhinney, D. B. Kaza, A. K. Mayer Jr, J. E.	J Thorac Cardiovasc Surg	2009	January 2002 -30 June 2007	274 AE reports in MAUDE, and 1537 cardiac surgery	Yes, MAUDE database	No	No	1
Application of a temporal reasoning framework tool in analysis of medical device adverse events	Retrospective study	Clark, K. K. Sharma, D. K. Chute, C. G. Tao, C.	AMIA Annu Symp Proc	2011	January 2009 to December 2010	15 reports were selected	Yes, MAUDE database	No	No	1
Automated surveillance to detect post procedure safety signals of approved cardiovascular devices	Retrospective study	Resnic, F. S. Gross, T. P. Marinac-Dabic, D. Loyo-Berrios, N. Donnelly, S. Normand, S. L. T. Matheny, M. E.	J Am Med Assoc	2010	April 2003 - October 2017	74,427 interventional coronary angioplasty procedures	Yes, Massachusetts angioplasty registry	Yes, DELTA	No	2

Title of Article	Type of Article	Authors	Journal	Year of Publication	Study Period	Number of Participants or Number of Reports	Post-Market Data Sources Medical Devices	Signal Detection Methodology for Medical Devices	Coding Dictionary for Medical Devices	Completeness Score
Cochlear implant complications: utility of federal database in systematic analysis	Retrospective study	Tambyrajaa, R. R. Gurman, M. A. Megeerian, C. A.	Arch Otolaryngol Head Neck Surg	2005	Pre 1998 and 2002	654 events on cochlear implant in 2002 and 129 pre-1998	Yes, MAUDE database	Yes, DPA; Frequentist (chisquare)	No	2
Disproportionality analysis for signal detection of implantable cardioverter-defibrillator-related adverse events in the Food and Drug Administration Medical Device Reporting System	Review article	Duggirala, H. J. Herz, N. D. Caños, D. A. Sullivan, R. A. Schaaf, R. Pinnow, E. Marinac-Dabic, D.	Pharmaco-epidemiol Drug Saf	2012	NA	NA	Yes, MAUDE database	Yes, DPA - Bayesian (MGPS)	No	2
Early detection of an underperforming implantable cardiovascular device using an automated safety surveillance tool	Retrospective study	Hauser, R. G. Mugglin, A. S. Friedlman, P. A. Kramer, D. B. Kallinen, L. M. McGriff, D. M. Hayes, D. L.	Circ Cardio-vasc Qual Outcomes	2012	November 2001 until December 2008	1035 Fidelis and 1675 Quattro leads	Yes, database of Sprint Fidelis and Quattro Secure implantable cardioverter defibrillator leads	Yes, DELTA	No	2

Title of Article	Type of Article	Authors	Journal	Year of Publication	Study Period	Number of Participants or Number of Reports	Post-Market Data Sources Medical Devices	Signal Detection Methodology for Medical Devices	Coding Dictionary for Medical Devices	Completeness Score
Estimates of medical device-associated adverse events from emergency departments	Retrospective study	Hefflin, B. J. Gross, T. P. Schroeder, T. J.	Am J Prev Med	2004	July 1999 through June 2000	10,395 medical device-associated adverse events	Yes, National Electronic Injury Surveillance System (NEISS)	No	No	1
Evaluating the Safety Profile of Non-Active Implantable Medical Devices Compared with Medicines	Review article	Pane, J. Coloma, P. M. Verhamme, K. M. C. Sturkenboom, M. C. J. M. Rebollo, I.	Drug Safety	2017	NA	NA	Yes, MAUDE, MEDSUN, MHRA, SCAAR, EUREQUO, AOANJRR,	No	Yes, Product problem: FDA and ISO Patient Outcome: SNOMED, MedDRA, ICD, FDA	2
FDA adverse event problem codes: Standardizing the classification of device and patient problems associated with medical device use	Review article	Reed, T. L. Kaufman- Rivi, D.	Biomed Instrum Technol	2010	NA	NA	No	No	Yes, FDA Adverse Event Problem Codes	1
FDA MAUDE data on complications with lasers, light sources, and energy-based devices	Review article	Tremaine, A. M. Avram, M. M.	Lasers Surg Med	2015	NA	NA	Yes, FDA MAUDE	No	No	1

Title of Article	Type of Article	Authors	Journal	Year of Publication	Study Period	Number of Participants or Number of Reports	Post-Market Data Sources Medical Devices	Signal Detection Methodology for Medical Devices	Coding Dictionary for Medical Devices	Completeness Score
Identifying optimal post-market surveillance strategies for medical and surgical devices: Implications for policy, practice and research	Review article	Gagliardi, A. R. Umoquit, M. Lehoux, P. Ross, S. Ducey, A. Urbach, D. R.	BMJ Qual Saf	2013	NA	NA	No	Yes, optimal post-market surveillance strategies for medical and surgical devices	No	1
Issues with medical device spontaneous reporting and improvements through MedSun	Review article	Ostuni, M.	Drug Inf J	2010	NA	NA	Yes, MEDSUN	No	No	1
Medical device regulation in Australia: Safe and effective?	Review article	McGee, R. G. Webster, A. C. Rogerson, T. E. Craig, J. C.	Med J Aust	2012	NA	NA	Yes, TGA	No	No	1
Methods and Issues to Consider for Detection of Safety Signals From Spontaneous Reporting Databases: A Report of the DIA Bayesian Safety Signal Detection Working Group	Retrospective study	Gould, A. L. Lystrig, T. C. Lu, Y. Fu, H. Ma, H.	Ther Innov Regul Sci	2015	Not specified	Not specified	No	Yes, review article that describes methods for signal detection	No	1

Title of Article	Type of Article	Authors	Journal	Year of Publication	Study Period	Number of Participants or Number of Reports	Post-Market Data Sources Medical Devices	Signal Detection Methodology for Medical Devices	Coding Dictionary for Medical Devices	Completeness Score
Mini-Sentinel's systematic reviews of validated methods for identifying health outcomes using administrative data: summary of findings and suggestions for future research	Review article	Carnahan, R. M.	Pharmaco-epidemiol Drug Saf	2012	NA	NA	Yes, Medicare	No	No	1
Participatory surveillance of diabetes device safety: A social media-based complement to traditional FDA reporting	Retrospective study	Mandl, K. D. McNabb, M. Marks, N. Weitzman, E. R. Kelemen, S. Eggleston, E. M. Quinn, M.	J Am Med Informatics Assoc	2014	October 2011 to September 2012	549 diabetes patients with device, 75 adverse events	Yes, online social networking community of people with diabetes and their caregivers or family members	No	No	1
Post-marketing surveillance of medical devices using medicare claims	Retrospective study	Malenka, D. J. Kaplan, A. V. Sharp, S. M. Wennberg, J. E.	Health Aff	2005	1 February and 31 November 2001	23,049	Yes, Medicare	No	Yes, ICD-9	2
Signal detection using change point analysis in post-market surveillance	Review article	Xu, Z. Kass-Hout, T. Anderson-Smits, C. Gray, G.	Pharmaco-epidemiol Drug Saf	2015	NA	NA	Yes, FDA MAUDE	Yes, multivariate method; change point analysis	No	2

Title of Article	Type of Article	Authors	Journal	Year of Publication	Study Period	Number of Participants or Number of Reports	Post-Market Data Sources Medical Devices	Signal Detection Methodology for Medical Devices	Coding Dictionary for Medical Devices	Completeness Score
The Data Extraction and Longitudinal Trend Analysis network study of distributed automated post-market cardiovascular device safety surveillance	Retrospective study	Kumar, A. Mathery, M. E., Ho, K. K. L., Yeh, R. W. Piemonte, T. C., Waldman, H. Shah, P. B., Cope, R., Normand, S. L. T., Donnelly, S., Robbins, S., Resnic, F. S.	Circ Cardiovasc Qual Outcomes	2015	January 2008 through December 2012	23,333 PCI cases	Yes, National Cardiovascular Data Registry (NCDR)	Yes, DELTA	No	2
The Kaiser Permanente implant registries: effect on patient safety, quality improvement, cost effectiveness, and research opportunities	Retrospective study	Paxton, E. W., Inacio, M. C., Kiley, M. L.	Perm J	2012	Not mentioned	Not mentioned	Yes, Kaiser Permanente Orthopedic implant registries	No	Yes, ICD-9	2
Towards a Prototype Medical System for Devices Vigilance and Patient Safety	Review article	Deligiannakis, A., Giatrakos, N., Pallikarakis, N.	2014 IEEE Symposium on Computational Intelligence in Health-care and e-health	2014	NA	NA	Yes, MEDICAL Devices Vigilance and Patient Safety (MEDEVIPAS)	Yes, multivariate method; entity matching algorithm	No	2

3.1. PMS Data Sources

Of the 21 articles including post-market data sources, 12 articles discussed SRS (one of the articles also included information on medical device registries), 9 articles discussed medical device registries (one of the articles also included information on SRS) and 1 article described a Non-Standard Data Source. Of the 12 articles including different SRS, the following SRS were discussed: FDA MAUDE database (US), TGA DAEN database (Australia), the future European Databank on Medical devices (Eudamed) (EU), MHRA database (UK), MEDSUN database (US), 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) (9–20) (see Table 3). Of the nine articles including registries, the following were discussed: 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 claims database constituting a person-specific registry of medical histories recording the use of all hospital services that are eligible for payment, including use of medical devices) (14, 21–28) (see Table 3). One article described a non-standard data source, namely, an online social

Table 3. Available PMS Data Sources for Medical Devices

Type of Available PMS data Source	Database
Spontaneous Reporting Systems (9-20)	• MAUDE (US, FDA), DAEN (Australia, TGA), Eudamed (EU, EC)
Registries (14, 21-24, 26, 27)	<ul style="list-style-type: none"> • Orthopedic: NJR (England, Wales and Northern Ireland), CJRR (Canada), KPOR (US), LROI (Netherlands), RNI (Brazil), AOANJRR (Australia) • Vascular: VQI (US), AVA registry (Australia and New Zealand), NVR (UK), JREAR (Japan) • Cardiac: SCAAR (Sweden), J-PCI (Japan), Cath-PCI (US), the US TVT (US), Japanese TVT (Japan), JACVSD (Japan), • Ophthalmology: EUREQUO (EU)
Non-Standard Sources (29)	<ul style="list-style-type: none"> • Safety networks: diabetes device safety network • Social networks: twitter, facebook, instagram, LinkedIn • Software devices: data entered by patients in mobile applications

Legend: MAUDE (Manufacturer and User Facility Device Experience), DAEN (Database of Adverse Event Notifications), TGA (Therapeutics Goods Administration), FDA (Food and Drug Administration), EU (European Union), EC (European Commission), NJR (National Joint Registry), CJRR (Canadian Joint Replacement Registry), KPOR (Kaiser Permanente Orthopedic Registry), LROI (Dutch Arthroplasty Registry), RNI (National Implants Registry), AOANJRR (Australian Orthopaedic Association National Joint Replacement Registry) SCAAR (Swedish Coronary Angiography and Angioplasty Registry), VQI (Vascular Quality Initiative), Australasian Vascular Audit (AVA), NVR (National Vascular Registry), JREAR (Japanese Registry of Endovascular Aneurysm Repair (abdominal and thoracic), PCI (Percutaneous Coronary Intervention), TVT (Trans-catheter Valve Therapies) JACVSD (Japan Adult Cardiovascular Surgery Database), EUREQUO (European Registry of Quality Outcomes for Cataract and Refractive Surgery)

networking community of people with diabetes and their caregivers or family members. This diabetes safety network captured data entered by patients in apps (see Table 3) and contained patient case reports of medical device events (29).

3.2. Signal Detection Methodologies

Ten articles described safety signal detection methodologies for medical devices, four articles discussed sign detection methodologies applied to SRS (9,12,19,20), four articles discussed signal detection methodologies applied to registries (22–24,26), and two articles discussed optimal signal detection methodologies for medical devices without applying the methodology to a specific type of PMS data source (30,31). No articles associated with signal detection methodologies applied to non-standard data sources were identified. Of the four articles using signal detection methodologies applied to SRS, two articles discussed disproportionate analysis (DPA) methodologies (Frequentist and Bayesian) (12,19), and two articles discussed multivariate methods (change point analysis and entity matching algorithm) (9,20). 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 (22–24,26).

3.3. Coding Dictionaries

Of the four articles that included information on coding dictionaries for medical devices, different dictionaries and nomenclatures were used, namely, FDA codes and International Organization for Standardization [ISO], IMDRF codes for product problems and investigation results, and Systematized Nomenclature of Medicine Clinical Terms [SNOMED CT], MedDRA, International Classification of Diseases [ICD], FDA Patient Problem and IMDRF Patient Codes for patient outcomes (14,25,27,32).

4. DISCUSSION

From this review, it is clear that spontaneous reporting systems and registries are primarily used for the medical device safety signal detection. Coding is remarkably diverse, no agreement on the preferred methods for signal detection currently exists, and no gold standard for signal detection has been established thus far. The main publicly available SRS are the FDA MAUDE (US), TGA DAEN (Australia) and the future EU Eudamed (EU) (33) (see Table 3; available PMS data sources for medical devices). The organization and content of each SRS varies, some are based on voluntary reporting and others on mandatory reporting, and usually track suspected medical devices, suspected patient harms or product problems, and patient data collected in a centralized and structured format (13). Per our literature review, the identified SRS are organized based on the relationship between medical devices and events. The data is

available for assessment and located in a repository or database (11,12,16,17,21). Nevertheless, SRS suffer from different limitations including: lack of harmonized global standard data set for reporting which makes integration of data from different databases challenging (14,34), difficulty to determine root causes for individual events conclusively due to limited information and no access to the actual device, with a large part of investigation results being inconclusive (35), missing and incomplete data that impacts the evaluation of the case, underreporting due to different reasons including lack of time, uncertainty about the medical device causing the adverse event, difficulty in accessing reporting forms, lack of awareness of the requirements for reporting, and lack of understanding of the purpose of SRS (36), and overreporting where medical devices with well-known adverse event/product problems are more likely to be reported based on influence from media coverage – the so-called notoriety bias (37). Despite SRS being a standard and required source for signal detection, we identified that medical device registries are important for signal detection as well and may also be used for risk quantification. Registries typically contain valuable information such as medical device information, diagnoses, medications, medical narratives and surgical interventions. Unlike spontaneous reports, medical device registries are not restricted to patients experiencing medical device product problems or patient harms. Therefore, medical device registries data provide some advantages that can be used to complement the more traditional PMS data sources (SRS), particularly the possibility to perform active PMS. In our literature search, we found that some retrospective studies have demonstrated the feasibility of an early warning detection system using medical device registries. For example, it has been demonstrated that the fracture of the Fidelis implantable cardioverter defibrillator (ICD) leads that caused inappropriate ICD shocks could have been detected much earlier if a medical device registry would have been created (19,22). Our literature review identified different types of methodologies (depending on the type PMS data source used) that can be applied to calculate reporting associations for all medical device-event combinations. Disproportionality analysis (DPA) was used as the main signal detection method for SRS – some used frequentist and other Bayesian approaches (12,19). These methods are well established for signal detection in drug safety. For complex types of SRS analysis, multivariate approaches have been proposed: change point analysis (20) or entity matching algorithm (9). These are not yet used for medical device safety signal detection. Methods applied to medical device registries can be categorized into those based on modified DPA ported from spontaneous reporting, and those based on the DELTA network methodology (22). Signal detection methods applied to medical device registries based on the Data Extraction and Longitudinal Trend Analysis (DELTA) network are considered automated safety surveillance tools that can competently support the detection of new potential post-market safety issues (15), complementing existing signal detection strategies and providing an additional tool to evaluate the safety of marketed medical devices (26). Our literature review demonstrated that different types of coding dictionaries used for medical device signal detection currently exist; for patient harms, product problems and evaluation/investigation

codes (methods, results and conclusion of the investigation). These coding systems are very heterogeneous. We conclude that there is a lack of standardization of medical device event coding across different jurisdictions. Furthermore, no mapping between some of the coding dictionaries currently exists. This issue could eventually delay the timely generation of safety signals associated with a medical device event reported in jurisdictions using different event coding dictionaries without an appropriate event code mapping.

4.1. Recommendations

Based on the analysis of the current literature on safety signal detection for medical devices and their limitations we have developed some recommendations (Table 4):

Table 4. Limitations and Recommendations on improving the Signal Detection for Medical Devices

	Limitation	Recommendation	Owner
PMS data sources: defragmentation and harmonization	SRS: Lack of a global database of spontaneous reports and lack of harmonization of required data set and reporting requirements across jurisdictions.	SRS: Creation of a global database of medical device spontaneous reports from national/regional databases to maximize the potential of data captured in Spontaneous Reports Databases. SRS: Define a common standardized data set for reporting individual device cases to be able to link global data, and develop consistent reporting requirements across jurisdictions to ensure the same type of reportable spontaneous reports are received globally.	IMDRF, HAs, WHO
	Registries: Lack of harmonization of medical device registries	Registries: Harmonization of registry networks by using the international Coordinated Registry Network (iCRNs). Registries: Define common data elements to be able to link the data.	IMDRF, HAs, WHO
Agreement on signal detection methodologies	There is no gold standard for the methodologies used for medical device signal detection.	Develop guidance on gold standard methodologies used to mine data from the different types of PMS data sources.	IMDRF, HAs
Standardization of coding dictionaries	Lack of harmonization and consistency of event codes used for patient harm, device problem and device evaluation codes.	Coding harmonization across all jurisdictions. IMDRF coding dictionary should be the gold standard used for coding purposes. HAs should adopt this new coding dictionary or map their national coding dictionary to the IMDRF coding.	HAs
	IMDRF codes are very high level with many events categorized as “no code available”.	Develop IMDRF coding guidelines classified by therapeutic area, and additional IMDRF codes to increase specificity, when appropriate. IMDRF needs to ensure maintenance of the IMDRF coding dictionary, and establish the right balance between having meaningful event code categories but not too much granularity.	IMDRF

Legend: HA (Health Authority), IMDRF (International Medical Device Regulators Forum), PMS (Post-market Surveillance), SRS (Spontaneous Reporting Systems), WHO (World Health Organization)

4.1.1. PMS Data Sources: Defragmentation and Harmonization

Currently different national SRS exist; however, no global database to access spontaneous reports on medical devices has been introduced. The inconsistency in post-market reporting requirements between regions leads to different levels of completeness that makes a comparison between different SRS databases challenging. The most significant one is adverse event reporting exemption applications in the EU (amongst other exemptions, expected side-effects are not reportable in EU but subject to event trending (8), in Canada (38) and Australia (18), however, no exemptions are applicable in the US (39)). Together with the standardization of SRS databases, harmonization of reporting criteria is needed. Otherwise, it will not be possible to identify signals from the National Competent Authority (NCA) SRS databases globally when some datasets completely exclude certain types of spontaneous reports. A multicomponent global database including reporting by manufacturers, clinicians and patients collecting spontaneous reports on adverse events related to medical devices, should be established for the assembly of all medical device reports from all National Spontaneous reports databases. The analysis of the collected data can then be performed by region or by country. In addition, harmonization of medical device registries databases is recommended. This harmonization could be established by using the international Coordinated Registry Network (iCRNs) to maximize the potential of information collected in the international registries.(1) The International Consortium of Orthopedic Registries (ICOR) is a good example of the effective use of a distributed safety data system with harmonized data definitions and data extraction followed by evaluating the data using innovative methodology across multiple national orthopedic registries. This decentralized structure system helps overcome issues related to security, operations, legal, and those related to patient privacy.(40) In order to link and potentially merge the data received from the different PMS data sources (SRS or registries), it is also recommended that guidance on common data elements and a common standardized data set for reporting individual device cases are developed (both for SRS and registries), and adopted by the different stakeholders involved in the process of collection and extraction of safety data for signal detection purposes.

4.1.2. Agreement on Signal Detection Methodologies

At this time, there is no agreement on the preferred methods for medical device signal detection for each of the different PMS data sources (SRS, registries and nonstandard data sources), and thus no gold standard has yet been established. IMDRF and Health Authorities should work together to develop guidance on gold standard methodologies that should be used to mine data from the different types of PMS data sources (SRS, registries and nonstandard data sources).

4.1.3. Standardization of Coding Dictionaries

To ensure more efficient signal detection we recommend the global adoption of the IMDRF coding dictionary by all Health Authorities. All the existing coding dictionaries will need to be mapped to the IMDRF coding dictionary to allow for an efficient system of signal detection

for medical devices. Taking into consideration that IMDRF codes are very high level with many events falling in the “no code available” category, we recommend IMDRF to develop a more granular level of coding developing additional IMDRF codes to increase specificity, when appropriate. In order to ensure consistency when selecting the appropriate codes, we also recommend the development of IMDRF coding guidelines classified by therapeutic area. IMDRF needs to ensure the maintenance of the coding dictionary, and establish the right balance between having meaningful event code categories while avoiding too much granularity. To ensure successful implementation of this new system, a global harmonized system for Unique Device Identifiers (UDIs) needs to be implemented, the UDIs need to be consistently assembled within PMS data, and all stakeholders need to ensure a continual use of the SRS and registries, including UDIs. The establishment of a global medical device identification database will aid in accomplishing this objective. The identification of devices during the signal detection process will continue to be a hurdle until the UDI is standardized and widely utilized for some time. This is a long-term goal because it involves significant policy change. Active collaboration and support from all stakeholders will ultimately lead to the success of these recommendations.

4.2. Developments in recent years

4.2.1. PMS Data Sources

Recent research emphasizes that the underlying data received from the PMS data sources need to meet high quality standards to ensure a timely safety signal generation. The authors of a recent case study describe PMS data as one of the main important publicly available SRS for medical device safety signal detection: FDA MAUDE (35). This research outlines that the completeness and the quality of the spontaneous reports in FDA MAUDE can be improved. The authors, furthermore, highlight the difficulty to determine root causes conclusively for individual events due to limited information, and no access to the actual medical device, with a large part of investigation results being inconclusive. Amongst others, it is recommended to address these challenges by considering the possibility of enriching FDA MAUDE PMS data with data from active PMS data sources such as medical device registries. In order to be able to link the registry data with the spontaneous reports, common standardized dataset including UDI should be created.

4.2.2. Signal Detection Methodologies

The developments regarding the applicability of new methods to the safety signal detection of medical devices have been a wide research topic over the past few years. The research in the area of passive safety surveillance (the data-mining methods used for disproportionality analysis of medical device–adverse event combinations from SRS) has become a main research focus area. Recent developments associated with the signal detection methodologies used for medicinal

products have been applied to medical device signal detection (41); for example, the likelihood ratio test (LRT) method that is applied to perform passive safety surveillance of medicines has now been successfully used to perform passive safety surveillance of medical devices. LRT is a frequentist method based on multiple 2x2 tables. It compares the reporting rate of different adverse events for a given drug or medical device of interest. The LRT method has successfully been applied for safety signal detection purposes to medical device SRS, and can also be used as spatial-cluster signal detection for an adverse event of interest from medical device registries and other databases that have patient-level geographical information. Moreover, the LRT method was compared to other frequentists and Bayesian methods, and found to be the most conservative method when evaluating the total number of detected safety signals, given its ability to control for false-positive safety signals (42,43). A big effort has been made in developing signal detection methods for medical device safety signal in passive safety surveillance. However, challenges still exist for the development of new active surveillance methods (statistical signal detection methods for medical device registries, and other longitudinal databases) for monitoring the safety of new medical devices over time. In medicines, this effort is currently being undertaken by the Observational Medical Outcomes Partnership (OMOP) and FDA Sentinel Initiative:

- OMOP: The OMOP is a public-private partnership involving the FDA, multiple pharmaceutical companies and healthcare providers. OMOP conducts methodological research on active drug safety surveillance by evaluating the performance of safety signal methods and their ability to identify true drug-adverse event associations. OMOP established a common infrastructure to collect different types of observational data from post-market data sources around the world, and successfully developed and implemented a large-scale signal detection methodology applied to medicines (44).
- FDA Sentinel: The FDA Sentinel is an active surveillance program that was established in the US with the long-term objective to create a national electronic system for PMS of FDA-regulated medical products (drugs, vaccines, biologics and medical devices). Over time, Sentinel has developed the largest multisite distributed database in the world dedicated to medical product safety. This new approach can help public health officers (who depend on passive surveillance tools lacking in denominator information, ie, patient exposure data) in detecting safety signals related to medicines and medical devices, and therefore aid in the accurate comparative assessments of safety risks (45). The application of these methods in medical device safety signal detection may have the ability to address some of the challenges associated with active safety surveillance of medical devices. Further research is required to evaluate the potential applicability of these two initiatives to active safety surveillance of medical devices.

4.2.3. Coding Dictionaries

There have also been some initiatives to address some of the challenges associated with adverse event coding for medical devices. An IMDRF project has worked on linking IMDRF codes and MedDRA codes (46). Moreover, IMDRF has also developed the IMDRF adverse event terminology maintenance plan; a document describing how to add, modify or delete adverse event terms to the IMDRF coding dictionary (47). Although these projects have the potential to address some of the identified challenges, some work still needs to be completed. The development of IMDRF coding guidelines by therapeutic area, and the creation of additional IMDRF codes to increase the granularity of the IMDRF coding dictionary are crucial to enhance the current adverse event coding for medical devices.

5. CONCLUSIONS

We have shown that a wide range of PMS data sources, coding dictionaries and signal detection approaches are available for the detection and assessment of medical device problems and patient harms. Each of them offers unique opportunities that together can contribute to developing standards for robust, consistent and improved signal detection for medical devices. New detection methodologies have been developed to utilize data that has not been used in the past, allowing for the introduction of new proactive models of medical device surveillance. Despite the increasing evidence of the benefits of medical device registries for the purpose of signal detection, spontaneous reports will remain a key data source of post-market device data and therefore a relevant source of potential signals. Standardized methods applied to similar data sources will be required. Data quality and coding harmonization will need to be improved and the UDI system will need to be fully implemented to benefit from the potential of proactive systems for the safety evaluation of medical devices. In order to succeed, all stakeholders involved in the PMS system must actively support each other and collaborate. This system will use real-world evidence to support regulatory decision-making across all jurisdictions.

ETHICAL APPROVAL

The authors state that no ethical approval was needed.

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Josep Pane and Dorian Villegas are employees of Alcon. Laura Gamez and Irene Rebollo are employees of Novartis. Katia M.C. Verhamme reports working for a research group that received/receives unconditional research grants from Yamanouchi, Pfizer/Boehringer Ingelheim, Novartis, GSK, and Chiesi, none of which are related to the content of this manuscript. Miriam C.J.M. Sturkenboom reports being a principal investigator on post-authorization safety studies for Novartis, non-related to this study. The authors report no other potential conflicts of interest for this work.

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CHAPTER 5

**NEW TOOLS FOR SAFETY
SURVEILLANCE OF MEDICAL DEVICES**

5.1.

EU Post-market Surveillance Plans for medical devices

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Keywords: medical devices, pharmacoepidemiology, post-market surveillance plan, risk management, safety evaluation

ABSTRACT

Purpose: Recent public health safety issues involving medical devices have led to a growing demand to improve the current passive-reactive post-market surveillance (PMS) system. Various European Union (EU) national competent authorities have started to focus on strengthening the post-market risk evaluation. As a consequence, the new EU medical device regulation was published; it includes the concept of a PMS Plan.

Methods: This publication reviewed Annex III Technical Documentation on PMS and Annex XIV Part B: Post-market clinical follow-up from the new Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices.

Results: The results of the PMS activities will be described in the PMS plan and will be used to update other related documents. A modular approach to structure the contents of the PMS plan will help to consistently update other PMS information. It is our suggestion that the PMS plan should consist of a PMS plan Core and a PMS plan Supplement. The PMS plan Core document will describe the PMS system, and the PMS plan Supplement will outline the specific activities performed by the manufacturer for a particular medical device.

Conclusions: The PMS plan may serve as a thorough tool for the benefit-risk evaluation of medical devices. If properly developed and implemented, it will function as a key player in the establishment of a new framework for proactive safety evaluation of medical devices.

1. INTRODUCTION

A medical device is defined as “any instrument, apparatus, appliance, material, or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of diagnosis, prevention, monitoring, treatment, or alleviation of disease, replacement, or modification of the anatomy or of a physiological process, and control of conception”(1). Medical devices are a great resource for enhanced diagnosis and disease management.

Recent public health safety issues involving medical devices have highlighted the need to update the European Union (EU) medical device regulation (MDR). The Poly Implant Prothèse (PIP) breast implant scandal in 2012 affected thousands of women and damaged the confidence of the different stakeholders involved in post-market surveillance (PMS) of medical devices (2). More than 400 000 women around the world received PIP implants that were made of industrial-grade silicone gel, prone to rupture, leading to inflammation and irritation. Another incident in 2012 involving hip implants raised a public health concern: metal-on-metal total hip replacements were successfully implanted, but metal abrading against metal caused erosion and leaching of metal particles into soft tissue (3). Such metal debris weakens tissue and bone around the implant, leading to implant failure, requiring additional surgery. The manufacturers did not provide an adequate response to the competent authorities with regard to these adverse events and there was always the belief that they could have been avoided (4). As a consequence, various national competent authorities (NCAs) and other health organizations started focusing on strengthening post-market risk evaluation of medical devices. One of the important novelties in the new regulation on medical devices (EU) 2017/745, published May 5, 2017 is the concept of a PMS Plan for each medical device family (5). A regulation is a legal act of the EU that becomes immediately enforceable as law in all member states simultaneously. Regulations can be distinguished from directives which, at least in principle, need to be transposed into national law (6). The current Medical Device Directive (MDD) 93/42/EEC states that “The manufacturer shall institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase, including the provisions referred in Annex X, and to implement appropriate means to apply any necessary corrective action.” Annex X says that “The clinical evaluation and its documentation must be actively updated with data obtained from the PMS. Where a post-market clinical follow-up as part of the PMS plan for the device is not deemed necessary, this may be duly justified and documented”(7). Contrary to what happens with the new regulation, there are no instructions or guidance on the contents of the PMS plan and on how to implement this requirement in the current MDD 93/42/EEC although the concept of a PMS plan is mentioned. According to the new regulation, the PMS Plan will have to define the process for collecting, recording, and investigating complaints and reports from healthcare professionals, patients, and users on events suspected to be related to

a medical device. A PMS system that is correctly designed should allow for early detection of possible malfunctions and/or complications of medical devices that may occur only after years or even decades of usage and implement appropriate risk minimization measures. Today, many medical device manufacturers have a “reactive” PMS system that is based on the collection of post-market data received from spontaneous reporting of complaints and incidents. Unfortunately, there are few proactive PMS processes designed to actively gain knowledge on the safety and performance of the medical device through external sources like registries, electronic healthcare records, safety evaluation sites, claim databases, social networks, and literature (8).

Key points:

- The new European Union (EU) post-market surveillance (PMS) plan may serve as a thorough tool for the benefit-risk evaluation of medical devices.
- If properly developed and implemented, the EU PMS plan will function as a key player in the establishment of a new framework for proactive safety evaluation of medical devices

The new EU Regulation aims to reinforce key elements of the existing regulatory approach, including vigilance and market surveillance, at the same time ensuring transparency and traceability, to improve health and safety (5). The objective of this article is to describe the new EU Regulation on PMS of medical devices, to compare it with our experience in the drug area, and to provide recommendations for implementation.

2. PMS SYSTEM FOR MEDICINAL PRODUCTS AND MEDICAL DEVICES IN THE EU

2.1. Medicinal products

Manufacturers may submit a marketing authorization application to either European Medicines Agency (EMA) or to the NCAs of the member states. Authorization through the European Medicines Agency, also known as the centralized procedure, offers the benefit of a single assessment process and a marketing authorization valid throughout the European Economic Area. Authorization through the centralized procedure is mandatory for innovative medicines derived from biotechnology, orphan medicines, and new active substances for the treatment of acquired immunodeficiency syndrome, cancer, neurodegenerative diseases, diabetes mellitus, autoimmune diseases and other immune dysfunctions, and drugs targeting viral diseases (9). Similarly to medical devices, safety issues involving medicinal products showed a need for a more proactive risk management approach of medicinal products. This led to the development of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2E guidance on risk management planning. This guidance was implemented in EU regulation in 2005 in the form of the EU risk management plan (EU-RMP), which is a mandatory template document for the authorization dossier of innovative drugs licensed in the EU (10-12). The EU-RMP describes the important risks and areas of missing information, the activities intended to further characterize the safety profile, and the measures to minimize the risks.(13,14) The EU-RMP is updated throughout the product life cycle as studies are completed or new information becomes available that may change the benefit-risk balance (15). Significant variation exists in the requirements and execution of post-authorization safety studies (PASS) and additional risk minimization measures (16-19). This is partly because the EU-RMP is product-specific and strategies are tailored to be risk-proportionate (i.e. taking into account variables such as seriousness and severity of the risk, target population, and healthcare setting of use of the product) (20). However, some variation is also due to marketing authorization holders: there is no gold standard for an optimal risk management organizational structure, and it depends on the magnitude and complexity of the company's pipeline, economic and staffing limitations, and organizational commitment to patient-centeredness (21). Cross-functional review of the risk minimization programs is recommendable and inclusion of senior management in final approval. The Pharmacovigilance Risk Assessment Committee (PRAC), an EMA scientific committee responsible for the review of all aspects of risk management planning, has been instrumental to overseeing post-approval commitments, and has played a key role in centralizing all the efforts to design and evaluate PASS (22). Table 1 describes some of the lessons learned from the pharmaceutical world and provides recommendations for implementation of the PMS plan for medical devices.

Table 1. Lessons Learned from the pharmaceutical world and recommendations for implementation of the PMS plan for medical devices

Topic	Lessons Learned from the pharmaceutical world	Recommendations for implementation of the PMS plan for medical devices
Enforcement of post-approval commitments	Pharmacovigilance Risk Assessment Committee (PRAC) has played a key role to centralize all efforts to design and evaluate PASS; PRAC has been instrumental to enforce post-approval commitments related to PASS.	As part of the NB's oversight, there should be a centralized group responsible for monitoring and assessing the safety of medical devices. This group should include CA and notified bodies, and should enforce the completion of CE mark commitments; such as post-market studies or registries included in the Post-market Clinical Follow-up Plan.
Documentation, monitoring and enforceability of post-approval commitments	Implementation of the EU-RMP template triggered more proactive approaches and the documentation of many additional risk minimization activities. Enforceability of these post-approval commitments came from making these commitments conditions to the marketing authorisation of the medicinal product.	Implementation of an actual PMS plan template is also important to document the post-approval commitments (e.g.; post-market studies, risk minimisation activities). Enforceability of these post-approval commitments will come from making these commitments conditions to the marketing authorisation of the medical device and verification during the annual PMS audits performed by the notified body.
Inclusion of risks in the PMS documents	Only important risks (risks that have an impact on the benefit-risk balance) from the Safety Specification should be included into the Pharmacovigilance (PV) plan.	Regulator-led initiative to develop risk based approach guidances to recommend the inclusion of only important risks (risks that have an impact on the benefit-risk balance) in the PMS documents (based on ISO 14971). Due to the wide range of medical devices and the different levels of complexity, these documents should be product-specific.
Manufacturer's Organizational adaptation	Cross-functional review of the risk minimization programs and inclusion of Senior Management in final approval is recommended.	Cross-functional review of the PMS plan is recommendable. The final approval of the PMS plan should be made by the person responsible for regulatory compliance (PRRC) within the company.

Abbreviations: EU, European Union; NB, notified body; PASS, post-authorization safety studies; PRAC, Pharmacovigilance Risk Assessment Committee; PMS, post-market surveillance; PRRC, person responsible for regulatory compliance; RMP, risk management plan; PV, pharmacovigilance.

2.2. Medical devices

NCAs, notified bodies (NBs), and manufacturers are all involved in the European Conformity (CE) marking process that allows marketing of a medical device in the EU. The NB is an entity that has been accredited by an EU member state to assess whether a manufacturer's quality

management system procedures and product technical documentation meets certain standards described in the EU MDD.

With the NB's certificate, the manufacturer can then issue the declaration of conformity, and apply the CE Mark, which is required for sale in the EU. The conformity assessment can include inspection and examination of a product, its design, and the manufacturing environment and processes associated with it, including the safety evaluation of the medical device. NCA's exist in each European member state and are nominated by each government to monitor and ensure compliance with its provisions of the MDD 93/42/EEC. The NCA designates a NB to ensure that conformity assessment procedures are completed according to the relevant criteria. The authorized representative, designated by the manufacturers (there is only an authorized representative when the manufacturer is not based in the EU; when the manufacturer is based in the EU, the manufacturer is the direct point of contact), is legally responsible for compliance with the regulations and acts as the first point of contact for the EU authorities. It is the manufacturer's responsibility to ensure that their product complies with the essential requirements of the relevant EU legislation. Medical devices are classified based on the risk associated with them, using the classification rules listed in Directive 93/42/EEC Annex IX. The categories are Class I, Class IIa and IIb, and Class III, with Class III ranked as the highest. The higher the classification, the greater the level of assessment required by NBs. The classification is based on the intended purpose of the device and not the particular technical characteristics. There are different aspects that are being taken into consideration for classification: grade of invasiveness, duration of contact with the body, and local versus systemic effect (7,23). In order to obtain the CE mark that allows marketing of a medical device in the EU (24), the manufacturer is obliged to identify and describe the risks detected during the pre-market phase (1,5). The risk management file (RMF) of the medical device or its family should contain clear definitions of the hazardous situations associated with use of the medical device. In addition, it should also describe the potential harms associated with these situations as well as the applicable risk minimization measures to avoid or mitigate these harms in both patients and healthcare users. According to the new EU MDR for medical devices, a comprehensive RMF demonstrating a positive benefit/risk profile is conditional to marketing and required to be monitored post-marketing in a timely manner. The new EU MDR has additional requirements in PMS and Vigilance compared with the current MDD (Tables 2 and 3).

Table 2. Post-market Surveillance System: Comparison between the current Medical Device Directive (MDD) (7) vs the new MDR (5):

MDD PMS Key Principles	MDR additional PMS requirements compared to MDD
Systematic procedure to review experience gained from the market.	PMS Oversight: Notified bodies and Competent Authorities have increased post-market surveillance authority for unannounced audits, samples checks, and annual safety reports.
Obligation to report incidents and increase in trends.	Clinical Evidence: Manufacturers need to conduct clinical investigations and collect post-market clinical data as part of ongoing safety assessment.
	PMCF plan to be part of the PMS plan. One PMS plan and one PSUR per device/ device group/family.

Abbreviations: MDD, Medical Device Directive; MDR, medical device regulation; PMCF, the post-market clinical follow-up; PMS, post-market surveillance; PSUR, periodic safety update report.

Table 3. Medical Device Vigilance System: Comparison between Meddev 2.12-1 (25) vs the new MDR (5)

Topic	Meddev 2.12-1	MDR
What to report?	<ul style="list-style-type: none"> Incidents 	<ul style="list-style-type: none"> Serious incidents (equivalent to Meddev 2.12-1 “incident” terminology)
Reporting timelines	<ul style="list-style-type: none"> Serious public health threat: 2 days Death or unanticipated serious deterioration in state of health: 10 days Other Reportable incidents: 30 days 	<ul style="list-style-type: none"> Serious public health threat: 2 days Death or unanticipated serious deterioration in state of health: 10 days Other Serious incidents: 15 days
Periodic Summary Reports	<p>When agreed with the coordinating competent authority:</p> <ul style="list-style-type: none"> For similar incidents with known root cause or FSCA implemented For common, well documented incidents 	<p>When agreed with the coordinating competent authority:</p> <ul style="list-style-type: none"> For similar incidents with known root cause or FSCA implemented For common, well documented incidents
Report to	<ul style="list-style-type: none"> NCA 	<ul style="list-style-type: none"> Centralized electronic reporting in EUDAMED
Trend reporting	<ul style="list-style-type: none"> Trend reporting is used by the MANUFACTURER when a significant increase in events not normally considered to be INCIDENTs and for which pre-defined trigger levels are used to determine the threshold for reporting. 	<p>Mandatory reporting of:</p> <ul style="list-style-type: none"> Statistically significant increase in frequency or severity of non-serious incidents or expected side-effect that could impact risk/benefit ratio ‘statistically significant increase’ needs to be defined upfront in the Tech File as part of the PMS plan for the device <p>The EU Commission will perform trending and signal detection based on the data in Eudamed.</p>

Table 3. Medical Device Vigilance System: Comparison between Meddev 2.12-1 (25) vs the new MDR (5) (*continued*)

Topic	Meddev 2.12-1	MDR
Field Safety Corrective Action (FSCA)	<ul style="list-style-type: none"> The details of FSCAs are communicated by manufacturers to the National Competent Authorities via FSCA form and to the users in field safety notices (FSNs). 	<ul style="list-style-type: none"> The details of FSCAs are communicated by manufacturers to the National Competent Authorities via FSCA form and to the users in field safety notices (FSNs). The NCA may perform their own risk assessment, manufacturer has to provide the supporting documentation. The national competent authority may intervene in the manufacturer's investigation. The Field Safety Notice needs to contain the UDI and the manufacturer's SRN and needs to be uploaded in Eudamed. National Competent authorities may ask Manufacturers for corrective actions and will inform the NB, other Manufacturers and the EU Commission.
Periodic Safety Update Reports	<ul style="list-style-type: none"> Not included in the current guideline. 	<ul style="list-style-type: none"> Class I devices: PMS report updated when necessary, but at least every 5 years. Class IIa: Periodic Safety Update Report to be updated when necessary, but at least every 2 years. Class IIb (non-implantables): PSUR to be updated annually. Class IIb (implantables), III: PSUR to be updated annually and sent to the NB for evaluation. Analysis of post-market surveillance data. Description of preventive and corrective actions. Conclusion of the benefit/risk evaluation. Main findings of the PMCF report. Sales volumes, estimate of the population using the device, usage frequency of the device.

Abbreviations: CA, competent authority; EU, European Union; EUDAMED, European Database on Medical Devices; FSCA, field safety corrective action; FSN, field safety notice; MDR, medical device regulation; NB, notified body; NCA, national competent authority; PMCF, post-market clinical follow-up; PSUR, periodic safety update report; UDI, unique device identifier.

The new EU MDR states that the PMS plan “shall be suited to the actively and systematically gathering, recording and analysing relevant data on the quality, performance and safety of a device throughout its entire lifetime, and to drawing the necessary conclusions and to determining, implementing and monitoring any preventive and corrective actions”(5). Table 4 specifies the main technical requirements of the PMS plan. The final approval of the PMS plan should be made by the person responsible for regulatory compliance (PRRC) within the company. To understand the key differences between the flow of risk management documents for a medical device and a medicinal product, it is important to understand the main differences between medical devices and medicines during new product development (Figure 1) and the main differences during the development pathway (Figure 2) (8). Figure 3 describes the flow of risk management documents that are required for a medical device and a medicinal product. One of the key differences between the two products is the filtering performed for medicinal products: only important risks (risks that have an impact on the benefit-risk balance) from the safety specification should be included into the pharmacovigilance (PV) plan. For

medical devices, there are no regulatory documents that provide guidance on filtering the risks from the RMF into the PMS plan. The RMF of a medical device includes the risk analysis, the risk evaluation, the implementation and verification of the risk control measures, and the assessment of the acceptability of any residual risk. Another difference with regard to medical devices is that the RMP of a medicinal product needs to be reviewed and approved by regulatory authorities, whereas the RMF or the PMS plan of a medical device are reviewed by the NB and do not require approval from the NCA. Contrary to what happens with medicinal products where the process goes through the EMA, or the designated NCA, in EU, the medical devices do not need to be approved by the NCA. In EU, the new medical device application (if required) is performed by the NB—an entity that examines the medical device application to assure compliance with the EU regulation. If the device meets regulatory requirements, a CE is applied, and the medical device can be marketed throughout Europe (26).

Table 4. Essential Requirements from the EU regulation for medical devices that are relevant to the Technical Documentation on Post-Market Surveillance – Extract of the EU regulation (5).

EU MDR (Annex III Technical Documentation on Post-Market Surveillance):

The manufacturer shall prove in a post-market surveillance plan that it complies with the obligation referred to in Article 83

(a) The post-market surveillance plan shall address the collection and utilization of available information, in particular:

- Information concerning serious incidents, including information from periodic safety update reports (PSURs), and field safety corrective actions (FSCA);
- Records referring to non-serious incidents and data on any undesirable side-effects;
- Information from trend reporting;
- Relevant specialist or technical literature, database and/or registers;
- Information, including feedbacks and complaints, provided by users, distributors and importers;
- Publicly available information about similar medical devices;

(b) The post-market surveillance plan shall include at least:

- A proactive and systematic process to collect any information referred to in point (a). The process shall allow a correct characterization of the performance of the devices and shall also allow a comparison to be made between the device and similar products available on the market;
- Effective and appropriate methods and processes to assess the collected data;
- Suitable indicators and threshold values that shall be used in the continuous reassessment of the risk benefit analysis and of the risk management as referred to in Section 3 of Annex I;
- Effective and appropriate methods and tools to investigate complaints or market experiences collected in the field;
- Methods and protocols to manage the events subject to trend report as provided for in Article 88, including the methods and protocols to be used to establish any statistically significant increase in the frequency or severity of incidents as well as the observation period;
- Methods and protocols to communicate effectively with competent authorities, notified bodies, economic operators and users;
- Reference to procedures to fulfil the manufacturers obligations laid down in Articles 83, 84, and 86;
- Systematic procedures to identify and initiate appropriate measures including corrective actions;
- Effective tools to trace and identify devices for which corrective actions might be necessary; and
- A Post-market clinical follow-up (PMCF) plan according to in Part B of Annex XIV, or a justification why a PMCF is not applicable.

Abbreviations: FSCA, field safety corrective action; PMCF, post-market clinical follow-up; PSUR, periodic safety update report.

	Discovery	Development	Preclinical	Clinical
Medical Devices	<p>Not always long and complex <i>(depends on the type of medical device)</i></p>	<p>Continuous, Incremental and Cyclical Process</p>	<p>Relatively Short <i>Usually does not include animal testing (except for biocompatibility testing)</i></p>	<p>Not always mandatory for all medical devices</p>
Medicines	<p>Long and complex <i>(years depending on the level of breakthrough technology)</i></p>	<p>Continuous, and usually Uni-directional process</p>	<p>Lengthy <i>Usually requires animal testing (preclinical trials)</i></p>	<p>Mandatory for all medicines</p>

Figure 1. Overview of the main differences during new product development between medical devices and medicines

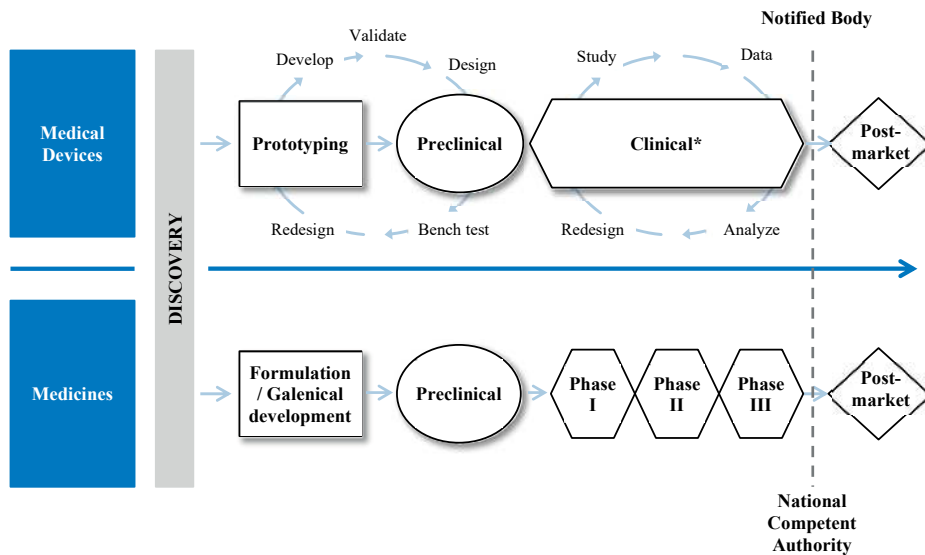


Figure 2. The medicinal product and the medical device development pathway in the EU

*Not always mandatory

Note: Some low risk (class I) medical devices may be “self certified” (without requiring a CE certificate from the NB) (25)

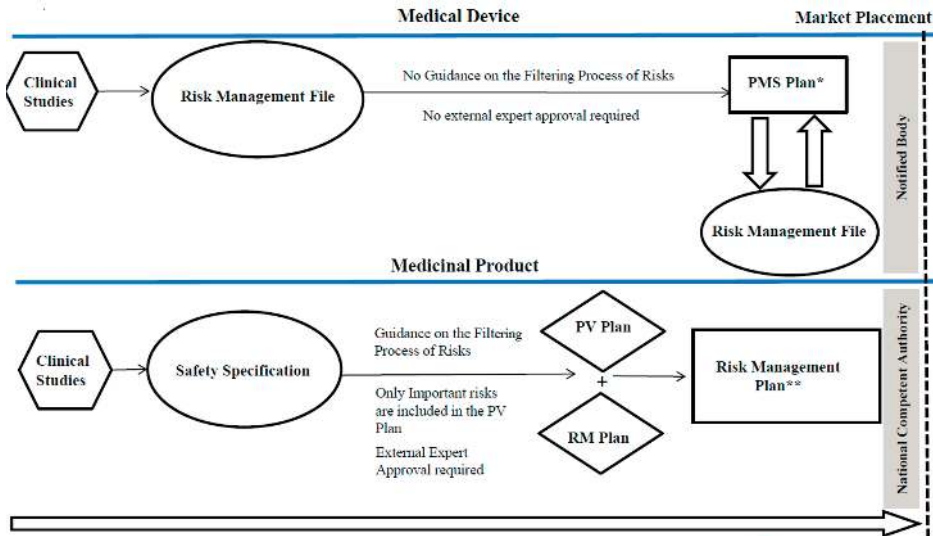


Figure 3. Risk managements documents required for the market placement of a medical device compared with a medicinal product.

*It includes description of processes and metrics

**Does not include description of processes and metrics. This information is included in the Pharmacovigilance System Master File (PSMF)

Note: In EU some low risk (class I) medical devices may be “self certified” (without requiring a CE certificate from the NB) (25)

3. RECOMMENDATIONS FOR IMPLEMENTATION OF THE PMS PLAN FOR MEDICAL DEVICES

Most of the current PMS requirements are included in the medical device guidelines, and not in the current MDD; this has led to enforcement challenges for the manufacturer’s requirements. With the new regulation, the EU wanted to eliminate those challenges and, at the same time, provide instructions on how to build a more proactive PMS system (Tables 2 and 3). Based on the requirements described in the new regulation and the lessons learned from medicinal products, we would like to propose the following recommendations for implementation of the new legislation. We have designed a template for the PMS plan content (see Tables 5 and 6). The PMS plan becomes a master file and consists of a PMS plan Core (Table 5) and a PMS plan Supplement (Table 6) containing different modules of PMS data. The Core document should describe the PMS system (routine PMS procedures, methodologies, and activities that are being performed for all medical devices or group/family of medical devices) as well as the key performance indicators (KPIs) used to evaluate the effectiveness of the plan. The Supplement should describe the specific PMS activities, methodologies, and procedures performed by the manufacturer for a particular medical device or family/group of medical devices.

Table 5. Suggested template: PMS plan Core

1. Post-market Surveillance	
Data Source	All data source for that medical device
Complaint Management (this would be part of the processes subsection)	Intake of an Adverse Event/Technical Complaint
	Medical Review
	QA Product Investigations
	Follow-up
	Submission/Reporting Process
Customer Feedback (subsection of source data)	Post-market Clinical Follow-up Plan (subsection of processes)
Monitoring of Product Benefit-Risk Profile (subsection of processes)	Adverse Event Trending
	Technical Complaint Trending
	Post-Production Information
Risk Management (subsection of processes)	Field Action Assessment Committee
	Device Medical Safety Review Board
	Safety Governance Review Board
2. Risk Minimization measures (part of the risk management)	
Communication of safety concerns	Safety Communication process
Effectiveness of risk minimization measures	Risk reduction process
Labeling Committee	Labeling risk minimization measures
3. Other PMS related processes and key SOPs	

Abbreviations: PMS, post-market surveillance; QA, quality assurance; SOP, standard operating procedure.

Table 6. Suggested template: PMS plan Supplement

1. Product Overview		
Product Name(s) / Family		
Approved Indication(s)		
Population being treated		
Medical Device Risk Classification		
License partners (if applicable)		
2. Summary of safety concerns		
Safety Concern	Hazard	Harm
Important Identified Risks		
Important Potential Risks		
Missing information		
3. Risk minimization measures		
Inherent safety by design and construction		
Protective measures in the medical device itself or in the manufacturing process		
Training to users and/or information for safe and proper use.		
Conduct of a study		
Communication of a FSCA		
4. Additional PMS activities		
Activity	Rationale	
5. Plans for Post-market Clinical Follow-up and Clinical Evaluation		
Summary of PMCF report (including registry review) and CER		
6. Safety Communications		
External and internal communication of safety concerns		
7. Annexes		
Training of Personnel		
Documents and Records		
8. References		

Abbreviations: CER, clinical evaluation report; FSCA, field safety corrective action; PMCF, post-market clinical follow-up; PMS, post-market surveillance.

The PMS Plan shall also define the frequency of the PMS data review. The manufacturer should institute a system to assess all the PMS information with a specific frequency and implement the necessary actions to improve safety and performance of the product. The Core and the Supplement should have different review timelines: the PMS plan Core only describes the processes and does not require a continuous update of the content. The periodicity of renewal of the PMS plan Supplement should be consistent with the risk associated to the product,

the innovative character of the device, and the level of clinical experience with the device. For example, as a general rule, classes IIb and III medical devices should be reviewed on a yearly basis and class IIa on a biannual basis (Note. Class I devices still need a review, but it is a simplified PMS supplement that should be updated at least every 5 years). The final approval of the PMS plan should be made by the PRRC. However, the PMS plan should also define who will review the PMS plan. We have learned in the drug era that the manufacturers should create an organizational model that ensures an efficient cross-functional review and senior management communication and the systematic incorporation of patient and healthcare professionals input into the PMS workflow. Key individuals from the different departments such as Medical Safety, Clinical, Research and Development, Regulatory Affairs, Compliance and Quality Assurance should participate in the production of the Core and Supplemental PMS plan. The final review of the documents should be performed by a cross-functional senior management team. Prior to launch, the manufacturer shall incorporate the risk minimization measures. The actual PMS plan and the activities involved with it may also lead to risk minimization measures such as a change in the labeling, a design change, or a material change. The new risk minimization measure will need to be documented in a consistent and timely manner across the other PMS documents (such as Risk Management and Periodic Safety Update Reports). This will be ensured by the use of the suggested modular approach (see Table 6) for the PMS plan structure. A program of appropriate PMS including post-market studies and registries is very important to detect and investigate risks associated with the use of marketed medical devices and should be included in the Post-market Clinical Follow-up (PMCF) plan. The plan describes methods for clinical data collection to confirm the safety and performance of a device throughout its lifetime; these methods may include post-market studies or registries as appropriate. Post-market studies and registries provide information on “real world” use and are a component of PMS. The post-market studies can be sponsor-led (sponsored by the manufacturer) or investigator- initiated trials (IITs) which are any scientific study, other than a manufacturer-sponsored study, originated and proposed by a third party investigator. Medical device registries can be sponsor-led or health authority-mandated and are designed for different purposes. They can offer valuable data on long-term effectiveness and safety of devices or on the impact of factors such as surgical method, physician, hospital, and patient conditions (27). It is important to take into consideration that data from these studies and registries need to be used for continuous evaluation of the benefit-risk profile as well as for discovery of new indications of use. When the PMCF study is completed, there should be a final report with clear conclusions that will be included in the periodic safety update report (PSUR). The results of PMS activities will have an impact on the PMS process during the device life cycle management. Some of the information from the PMS plan will be used to update other related PMS documents. A modular approach to structure the contents of the PMS plan may help to consistently update other PMS information. The output of the PMS plan could lead/affect different post-market documents (Figure 4). For example, after the review of national registries

(part of the PMCF up plan), the manufacturer may identify a new safety issue with the product that will affect different post-market documents: update of RMR, update of clinical evaluation report (CER), new PSUR, development of corrective and preventive actions (CAPAs), new training to the user, or submit a field safety corrective action (FSCA) to the NCA.

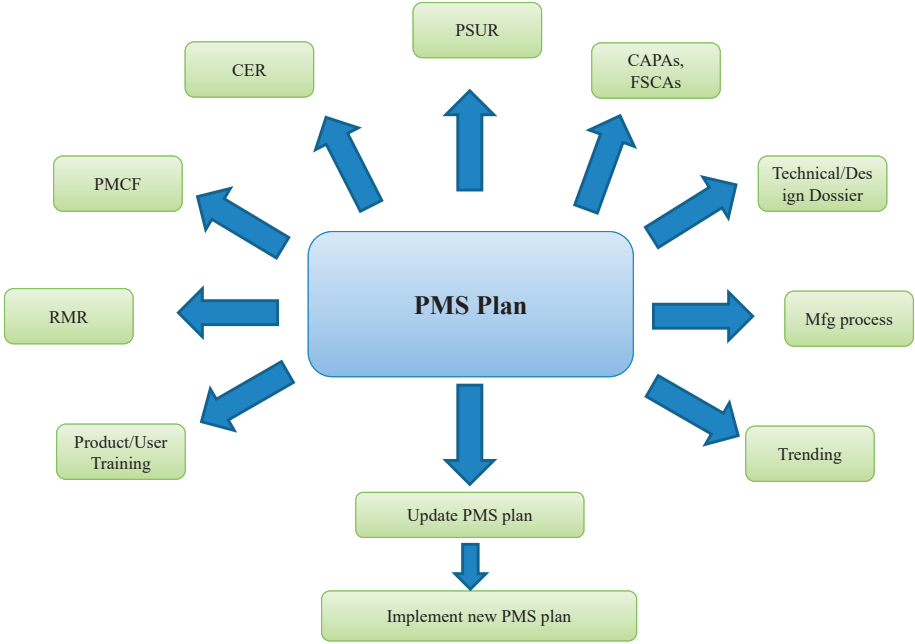


Figure 4. Output of the PMS plan.

To measure the effectiveness of the PMS plan, it is important to have adequate tools in place for each of the processes. KPIs must be identified a priori when building the processes. Moreover, together with the KPIs, it is essential to identify a threshold for each of the indicators to take action if this threshold is reached. Therefore, the key processes that need to be measured should be identified, and the significant points of measurement that define the performance of the systems should be described in the PMS plan. These measures will help to identify areas of improvement. In Table 7, we propose different KPIs to monitor the performance of the PMS system, there should be KPIs for case processing, safety communications, PSURs, risk management, early detection of signals, and implementation of corrective actions.

Table 7. Proposed Key Performance Indicators to measure effectiveness of PMS plan

Process	KPI	Type	
		Quality	Timeliness
1.- Case Processing	Expedited reporting on time	-	x
	Periodic Reporting on time	-	x
2.- Case Quality Review	Case Quality Review	x	-
	Quality review of regulatory reports	x	-
	Comments and Inquiries received from Competent Authority after the submission of a Regulatory Report	x	-
3.- Periodic Search of Scientific Literature	Literature Search Review timeliness	-	x
	Peer review of selected abstracts	x	-
	Peer review of rejected abstracts	x	-
4.- Aggregate Reports	PSUR submission timeliness to Competent Authorities	-	x
	Comments and Inquiries received from Competent Authority after the submission of PSUR	x	-
5.- Safety Communications	Safety Communications submitted on time	-	x
	Comments and Inquiries from Competent Authorities, healthcare professionals or consumers received after the submission of the safety communications	x	-
6.- Signal Detection	Signals detected on time; timely identification of safety issues	-	x
	Signal evaluation and validation performed effectively; real signal?	x	-
7.- Corrective Action	Corrective actions implemented on time	-	x
	Corrective actions effectiveness	x	-
8.- Risk Management	Risk Management File timely review; timely update of the risk management file	-	x
	Rates of comments and inquiries from Competent Authorities (CA) by impact	x	-

Abbreviations: CA, competent authority; KPI, key performance indicator; PMS, post-market surveillance; PSUR; periodic safety update report.

4. DISCUSSION

This paper tries to provide implementation guidance to the medical device EU regulation based on lessons learned from the medical product area. We have seen how vital it is to identify the risks in a timely manner for all stakeholders to be aware of the risks associated with medical devices. Stakeholders need to take appropriate corrective and preventive measures to improve patient outcome (3) resulting in a device that is safe and performs well. We conclude that the PMS plan needs to include the identified risks, potential risks, and missing information from the RMF. Next, safety evaluation tools (CER, PSUR, RMF) to find responses to unanswered questions and find more information regarding missing information should be implemented. The PMS plan should have clear objectives, a robust structure with specifications on data integrity, periodicity, and defined responsibilities. We recommend a modular approach to

structure the contents of the PMS plan that will facilitate consistent updating of other PMS information. The PMS plan should consist of a PMS plan Core and a PMS plan Supplement. The PMS plan Core document will describe the manufacturer's general PMS system, and the PMS plan Supplement will describe the specific PMS activities performed by the manufacturer for a particular medical device or family/group of medical devices. Since we learned from the medicinal products area that a template is important, we proposed one. In addition to the template, another important aspect learned from the experience with medicinal products is the methodology used to include customer feedback and the organizational structure within the company. To deliver high-quality PMS plans, companies need to implement a system that includes cross-functional review and takes into account the patient feedback received during the post-market phase. A difference with medicinal products is the fact that no filtering is implemented: we would recommend that the regulatory bodies develop product-specific guiding documents outlining how to perform the filtering of risks from the RMF to the PMS plan and also provide guidance on the stakeholder responsibility in reviewing and approving the PMS plan. Moreover, to ensure the success of the PMS plans, the manufacturers should first identify the key processes of the plan and define KPIs as well as the associated thresholds to take action. These indicators will help to measure the effectiveness of the plan. In conclusion, the new EU MDR may positively impact medical device safety evaluations and calls for a more hands-on approach, which does not only consist of spontaneous reporting, but also includes proactive methods to manage product-related risks with new safety evaluation tools such as the PMS plan. There are several questions regarding the implementation of the new EU medical device guideline and differences with medicinal products. This paper tries to review them and provide some guidance.

ABBREVIATIONS

CAPA: Corrective And Preventive Action

CER: Clinical Evaluation Report

EU: European Union

FSCA: Field Safety Corrective Action

HCP: HealthCare Professional

KPI: Key Performance Indicator

MDR: Medical Device Regulation

NCA: National Competent Authority

NB: Notified Body

PASS: Post-Authorisation Safety Studies

PMCF: Post-market Clinical Follow-Up

PMS: Post-market Surveillance

PIP: Poly Implant Prothèse
PRAC: Pharmacovigilance Risk Assessment Committee
PRRC: Person Responsible for Regulatory Compliance
PSUR: Periodic Safety Update Report
PV Plan: Pharmacovigilance Plan
QA: Quality Assurance
RMA: Risk Minimization Activities
RMF: Risk Management File
RM Plan: Risk Management Plan
RMR: Risk Management Report
SOP: Standard Operating Procedure

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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CONFLICT OF INTEREST

Josep Pane and Marcia Orozco are employees of Alcon, which manufactures medical devices. Irene Rebollo is an employee of Novartis, which manufactures medical devices. Hilde Viroux is an employee of HCL Technologies, an engineering services company, active in many areas including medical devices. Reynold Francisca, Katia Verhamme, and Miriam Sturkenboom have no conflicts of interest that are directly relevant to the content of this manuscript.

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CHAPTER 6

**NEW TECHNOLOGY APPLICATIONS TO
SAFETY SURVEILLANCE OF MEDICAL
DEVICES**

6.1

Blockchain technology applications to Post-market Surveillance of Medical Devices

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Keywords: blockchain, medical devices, post-market surveillance, safety evaluation, risk management

ABSTRACT

Introduction: The amount of mandatory data that needs to be analyzed as part of a medical device post-market surveillance (PMS) system has grown exponentially in recent times. This is a consequence of increasingly demanding and complex regulatory requirements from Health Authorities, aimed at a better understanding of the medical device safety evaluation. Proactive approaches to PMS processes are becoming more necessary as regulators increase the scrutiny of device safety. New technologies have been explored to address some of the challenges associated with this changing regulatory environment.

Areas covered: This paper focuses on the different technical aspects of blockchain and how this new technology has the potential to support the ongoing efforts to improve the PMS system for medical devices.

Expert opinion: To address these challenges, we suggest to generate a private PMS data permissioned blockchain with a proof-of-authority consensus mechanism, for which only a restricted number of designated and audited participants have authorization to validate transactions and add them to the PMS data blockchain ledger. Blockchain has the potential to support a more efficient approach, which could offer many advantages to the different stakeholders involved in the PMS process, including supporting with new regulatory initiatives.

Article Highlights

- Proactive approaches to post-market surveillance are becoming more necessary as regulators increase the scrutiny of medical device safety.
- Blockchain technology has the potential to solve some of the current challenges associated with the safety surveillance of medical devices by supporting device traceability, and efficient safety data exchange while maintaining data privacy, integrity and accessibility.
- Recommendations on how to address identified challenges related to the use of blockchain in the safety surveillance of medical devices are presented with a focus on solutions associated with data privacy, data storage, data exchange and data standardization.
- The suggested private post-market surveillance data permissioned blockchain with a proof-of-authority consensus mechanism as well as the proposed step-wise implementation process are the foundation of the future blockchain-based safety surveillance system for medical devices.
- A solid knowledge of the current challenges and needs of the medical device industry, and continuous collaboration with blockchain technology experts will ultimately lead to the successful implementation of blockchain in the post-market surveillance of medical devices.

1. INTRODUCTION

The amount of required data that needs to be analyzed as part of a medical device post-market surveillance (PMS) system has grown exponentially in recent times. This is a consequence of increasingly demanding and complex regulatory requirements from Health Authorities, aimed at a better understanding of the medical device safety evaluation. One of the main goals of the new regulations is to ensure a rapid, reliable and efficient exchange of PMS data to ensure medical device safety issues are identified in a timely manner, and appropriate action is taken accordingly. Proactive approaches to PMS processes are becoming more necessary as regulators increase the scrutiny of device safety (1,2). This has led many of the stakeholders involved in the process of safety evaluation of medical devices to explore solutions to address some of the challenges associated with this changing regulatory environment. Furthermore, they understand the need to respond to some of the gaps associated with this process (3,4). As in any other field of the medical device industry, the stakeholders have started working on artificial intelligence (AI) solutions that could help change the current reactive medical device PMS system. Some of the solutions that have been explored thus far in the area of medical devices include machine learning, robotic process automation, Internet of things and blockchain. Later will be described briefly Blockchain technology has gained a high degree of attention over the past 2 years (5). Blockchain can be understood as serving its users as a circulated database. That database permits its users to process data via specific nodes attached to the network. The traditional data exchange approach would have users maintain data via a centralized authority. Blockchain decentralizes that process and allows users to transact with one another without a third-party intervention, which is a major benefit of the blockchain process. As an example, let user C represent the so-called third party such as a governmental or healthcare regulatory body. Traditionally, if user A and user B wish to transact, user C would get involved to authenticate the identity of both users. However, in the blockchain setting, there is no more necessity for user C to intervene. The blockchain environment has led the way to new opportunities for transactions: a user may use blockchain technology to digitize, code and insert virtually any transaction of information in an immutable, distributed and secure manner. In this paper, we will focus on the different technical aspects of blockchain and how this new technology has the potential to support the ongoing efforts to improve the PMS system for medical devices.

2. BLOCKCHAIN TECHNOLOGY

A blockchain is a decentralized, distributed, and oftentimes public, digital ledger that is used to record transactions across many computers so that any involved record cannot be altered retroactively, without the alteration of all subsequent blocks (6). Blockchain is a technology based on public secure communication to track historical transactions related to distributed

patient records. For example, Blockchain technology can offer efficient safety data exchange while maintaining data privacy, integrity and accessibility. This new technology could make available substantial quantities of anonymous PMS data from different sources (spontaneous reports, medical device registries, nonstandard data sources). Blockchain enables multiple parties within a network to share a single ledger, which all parties can trust as valid. Each new piece of data (transaction) is included in a ‘block’, each block containing a hash of the prior block, connecting it to its predecessor and creating a chain of blocks – or blockchain. The network timestamps transactions by hashing them into a continuous chain of hashbased proof-of-work, creating a record that cannot be altered without redoing the proof-of-work (7). These recorded transactions may be used to support currencies and payments but also safety data (8) (see Table 1). A node that is part of this network has to verify each new transaction to ensure its completeness. As each transaction in a block of a blockchain is verified by all of the nodes in the network, it becomes more immutable with every block added to the chain. The diagram below shows the workflow of the blockchain process (as shown in Figure 1). There are different levels of verification of ledgers. A public blockchain has ledgers that can be viewed by anyone, and anyone can verify and add a block of transactions to the blockchain (9). A private blockchain allows only specific individuals in the organizations to verify and add transaction blocks but everyone on the internet is generally allowed to view them, depending on the type of blockchain (10). Consortium: only a specific type of group within the organization (such as banks) can verify and add transaction but the ledger can be opened or restricted to the selected group (11).

Table 1. Key features of blockchain:

Key features	Functionality Description
Immutable	Blockchain is an immutable record that is distributed across multiple computers. The computers in the system compete to have the ability to add a new block (mining). Each block contains the prior block’s hash. The blocks become reserved forever, and cannot be altered easily without having control of more than 51% of the nodes simultaneously.
Distributed	Blockchain does not have a controlling authority of the data. Participants prove themselves through Proof of Work or Proof of Stake. The data can be accessed, and updated on multiple computers.
Transparent	The data on blockchain is transparent to users, and can be further updated easily. The transparent nature of blockchain prevents data from being modified.
Autonomy	Each node on the blockchain system can store, transfer, and update the data securely, without any external interference.
Open Source	Blockchain offers an open source access to all the stakeholders connected to the network.
Anonymity	As data transfers from one node to another node, the identity of the individual during the data transfer remains anonymous.

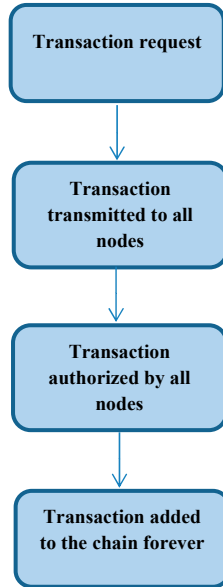


Figure 1. Workflow of the blockchain process

3. CHALLENGES RELATED TO ADEQUATE POST-MARKET SURVEILLANCE OF MEDICAL DEVICES

The following issues have been identified as challenges associated with implementation of adequate post-market surveillance of medical devices:

3.1. Security & exchange of data

With a growing number of new technologies that connect medical devices, there is a potential for hacking of PMS data, which should be prevented (2,3). A secure environment for data exchange is required to ensure rapid sharing with appropriate stakeholders. The timely exchange of PMS data throughout the different PMS data sources and PMS documents is one of the main challenges associated with the safety signal detection process for medical devices. The failure to promptly identify safety issues associated with marketed medical devices has recently led to public health scandals (12,13).

3.2. Medical device traceability

The identification of the root cause of the adverse event is crucial for a robust PMS system. In order to identify the root cause, the evaluation of the medical device sample is key to isolate the failure mode associated with the event, and is often lacking (4).

3.3. Counterfeit

Counterfeiting medical devices is a well-known threat to patient safety (14). To address this issue, there has been an increasing regulatory demand for more information about the medical device origin (1).

3.4. Regulatory actions

To execute regulatory actions related to safety, it is required to quickly identify the location of all the medical devices in the market, which requires a Unique Device Identifier (UDI) (4).

3.5. Standardization

One of the main challenges during the safety signal detection of medical devices is the lack of standardization and harmonization of PMS data sources. Each PMS data source contains different content and uses a different methodology to store the data (3). Two of the main types of medical device PMS data sources are Spontaneous Reporting Systems (SRS) and medical device registries. These two data sources have its own benefits and limitations:

- Spontaneous Reporting Systems: SRS are reactive systems that contain reports of patient harms and product problems collected from healthcare professionals, patients, healthcare authorities and manufacturers whether reported directly or through published articles. SRS are organized based on the relationship between medical devices and events. The data collection cover large populations and their processing is centralized normally in a repository or database where they are available for assessment (15,16,17,18,19). Nevertheless, SRS suffer from different limitations including: lack of harmonized global standard data set for reporting which makes integration of data from different databases challenging (3,20), difficulty to determine root causes for individual events conclusively due to limited information and no access to the actual device, with a large part of investigation results being inconclusive (4), missing and incomplete data that impact the evaluation of the case, underreporting and over-reporting where medical devices with well-known adverse event/product problems are more likely to be reported than other medical devices based on influence from social network, or media coverage (21).
- Medical Device Registries: A medical device registry is defined as an ‘organized system with a primary aim to increase the knowledge on medical devices contributing to improve the quality of patient care that continuously collects relevant data, evaluates meaningful outcomes and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale (e.g. international, national, regional, and health system)’ (22). Medical device registries typically contain valuable information such as medical device information, diagnoses, medications, medical narratives and surgical interventions. Unlike spontaneous reports, medical device registries are not restricted to patients experiencing medical device product problems or patient harms. Therefore, medical device registries data provide some advantages that can be used to complement the more

traditional PMS data sources (SRS), particularly confirmatory studies and the possibility to perform active PMS (23,24). Although the use of medical device registries presents many advantages, it also presents certain challenges:

- o Lack of standardization: the characteristics of the registry might vary across countries with differences in granularity, consistency and quality of data, duration of longitudinal follow-up, attrition rates, data privacy standards, regulation, ability and level of information exchange (25). This lack of standardization between the different registries may lead to a possible delay before PMS data from international registries is collected and consolidated, eventually causing a delay in safety signal verification (22).
- o The lack of use of a harmonized UDI and nomenclature codes impacts the analysis of device outcome information from the registry (26).

3.6. User training

A key contributing factor to adverse events with medical devices is the user error (3). Development of appropriate risk mitigation activities, mainly training, is essential to ensure safe handling of medical devices.

4. OPPORTUNITIES FOR USE OF BLOCKCHAIN TECHNOLOGY TO ADDRESS CHALLENGES IN MEDICAL DEVICE PMS SYSTEM

For medical device PMS we see potential for a public permissionless blockchain, and for a private permissioned blockchain, which may address several of the challenges that have been mentioned above (see Table 2).

4.1. Medical device traceability

Blockchain technology may very well support the global implementation of UDI. Blockchain enables the recording of data of all production and ongoing usage or maintenance. Its immutable and reliable workflow will support the medical device manufacturers with complete traceability and provide evidence on any safety issue associated with the specific medical device. This type of technology is becoming more relevant following the additional traceability requirements (Articles 25 and 27 of the EU MDR) (1), which will come into place in May 2021. The new regulation requires an UDI to be included on all product packaging in both human-readable and machine-readable form. Annex VI of the MDR discusses the usage of automatic identification and data capture tools such as QR codes or bar codes, which could eventually be used in conjunction with blockchain technology. Machine-readable information can be encoded within a bar code, and potentially include access to a blockchain traceability

Table 2. Applications of blockchain technology in PMS of medical devices

Gap in Medical Device PMS	How blockchain can address this gap
Medical device traceability	Blockchain technology could support the global implementation of UDI.
Regulatory actions and counterfeit	Blockchain can be used to track and monitor regulatory actions related to the market release of devices, and will also help to verify medical device counterfeiting.
Security, standardization and exchange of PMS data	Blockchain can provide a secure real time exchange of PMS data, which could be part of the distributed ledger of an approved blockchain. The integration of blockchain in PMS has the potential to standardize the content and the format of PMS data sources, and create a more efficient protected PMS data exchange process.
User errors	Blockchain can fastly identify different type of user errors in a faster manner, and find the training required to address the type of user error.

system within the one bar code (27). The blockchain traceability tool serves in the recording of each step of the supply chain and interaction with the product. Any economic operator, who is engaged with that medical device, would have access to the blockchain and thus would be able to review the interactions of that medical device. This activity will make important data efficiently available to the health authorities. By reading the blockchain, end-recipients could autonomously confirm that a medical device is genuine by confirming its authenticity against the UDI database and through the supply chain. Article 28 of the new MDR requires that the UDI database warrants ‘maximum accessibility to information stored therein, including multi-user access’ and which shall ‘validate, collate, process and make available to the public (the information)’. The regulation requires ‘appropriate methods ... for validation of the data provided’ and that ‘manufacturers ... periodically verify the correctness of all of the data relevant to devices they have placed on the market’ (1). A blockchain-based repository could provide some of the functionalities the regulators require.

4.2. Regulatory actions & counterfeit

The global adoption of UDI (4), and blockchain technology could improve the efficiency of the regulatory action coordination process by tracking all the medical devices that are on the market to ensure fast and efficient removal from the market. Through its ability to track all transactions, blockchain technology is able to monitor every stage of the medical device supply chain. Blockchain will reinforce data integrity and improve medical device traceability across the supply chain, and will also help to verify medical device counterfeiting.

4.3. Security, standardization & exchange of PMS data

The immutability of Blockchain supports fraud detection by prohibiting any replication or alteration in the transaction, leading to a transparent, reliable and secure record. Blockchain may support a more proactive approach to collect PMS data (spontaneous reports, registries, nonstandard data sources, etc.), by allowing to directly obtain data without the need to ‘actively report’ the adverse event; e.g. a patient entry in a medical device registry is completed, or a healthcare professional enters information on an adverse event related to a device in an electronic health record. This could become a block of data that is shared when the relevant data fields are entered, without the need to actively choose to report an adverse event. This initiative could lead to an increased amount of post-market data with limited human interaction that would eventually lead to better quality of collected PMS data. Blockchain provides a distributed secure framework for any exchange of safety data. This type of framework is not part of a central group ‘controlling’ its accesses and, therefore less likely to be affected by a cyberattack. The nature of distribution of blockchain could help to maintain PMS data in a more systematic way, and provide permanent secure storage of medical device PMS data through new storage solutions which enable users to store PMS data in a platform that live forever on a blockchain, all while keeping the speed high and a low monetary cost low. The PMS data could be part of the distributed ledger of an approved blockchain. The integration of blockchain in PMS has the potential to standardize the content and the format of PMS data sources, and create a more efficient protected PMS data exchange process (28), guarantee data integrity and transparency, and eliminate any human intervention; from data creation to data retrieval. The involvement of many and unrelated participants strengthens the integrity of the chain by decreasing the risk of collusion to modify data. This risk is reduced due to the fact that consensus is mandatory to change the chain. Although the PMS data on a public blockchain would be secure and the identity of the participants would be pseudonymized, the data would not be private. Instead, data would be transparent for all participants to review. To enable privacy, ‘private’ blockchains should be developed, so that only certain stakeholders can participate, review and modify the blockchain. This type of ‘private’ blockchains could be used for the exchange of PMS data between the different stakeholders involved in the process of safety evaluation of medical devices.

4.4. User errors

Blockchain technology can support the identification of safety issues for software devices related to user error in a faster manner informing the manufacturer on the type of user error and identifying the training required to address the type of user error.

5. CHALLENGES IN USE OF BLOCKCHAIN TECHNOLOGY

In order to ensure the successful implementation of blockchain in the PMS process of medical devices, it is crucial to understand the challenges associated with the use of this new technology (Table 3).

5.1. Security and privacy of data

Blockchain provides a higher level of security as the need for a third-party involvement in the completion of the transaction of safety data is eliminated. Nevertheless, the data becomes vulnerable to potential privacy and security risks as the mechanism of blockchain allows the entire community of users, rather than a single third party, to verify the records in a blockchain architecture (5). Since all nodes are able to view the data transmitted by one node, data privacy cannot be ensured. Absence of a third party for approval requires the patient to pick one representative that can view his information, in the case of an emergency. This representative may allow other individuals to access the records of the same patient, which may generate a significant data privacy and security risk. The alternative option would be to create highsecurity mechanisms to the data, but this would result in obstacles in transferring the data from one block to another and, thus, lack of access of data. In addition, blockchain networks are vulnerable to a kind of security breach known as 51% attack (29,30). This attack consists of a group of miners that collectively own more than 50% of the nodes in a blockchain network and collaborate to alter the blockchain data. The miners get an authority of the network and could prevent the completion of any new transactions by not authorizing them with the consent. Five cryptocurrencies have recently been a victim of this attack (31). Lastly, another challenge associated with the use of blockchain with PMS is that a patient record might have sensitive data that is unsuitable to be on the blockchain (32). To address these challenges, we suggest to generate a private PMS data permissioned blockchain with a proof-of-authority consensus mechanism, where only a restricted number of designated and audited participants have authorization to validate transactions and add them to the PMS data blockchain ledger. Alternatively, we could recommend a reliable decision-making setting: for example, using the blockchain-based system called MedRec (33), patients/healthcare professionals/ manufacturers/health authorities can approve the addition of new members to the private blockchain, protect and identify the members of the PMS community responsible for approving changes, and govern the sharing between the different stakeholders. This enables members of the PMS community to add a new record associated with a specific patient, and patients can approve sharing of records between different stakeholders. There is prioritization of use in all user-stakeholder interactions, and this will provide a single database to review any updates to patients' medical history. In addition to enhance PMS stakeholders control over PMS data sharing, this proposal could also remove one of the main obstacles during exchange

of PMS data which is data reliability (28). Yet another solution would be to ensure full data privacy to participants during the PMS data transaction, while still being able to validate the authenticity of the transaction. However, some of the participants in our private blockchain could be medical device manufacturers. The conventional blockchain application would allow participants to obtain sensitive private data about their competitors. To eliminate any risk of competitors acquiring sensitive information about each other, our PMS private blockchain should build a zero-knowledge proof algorithm mechanism ensuring that competitors cannot see the transaction data of their competitors, while allowing transactions to be validated (34).

5.2. Manage data storage

Another challenge is the management of data storage capacity. The traditional web and its data storage systems are fragile and liable to potential data losses. Contrary to what happens with the traditional centralized data storage systems, blockchain offers a distributed tool to store the data. Blockchain is designed to track and complete the transaction of data. However, PMS has a large amount of data that must be stored on a regular basis (35). All the PMS data in the blockchain should be available to all the nodes in the chain, which needs a great storage capacity (6,36). Due to growing number of PMS databases, the rapidity of event searching and editing can be low and this could represent a challenge, which is highly unsuitable for the PMS data transactions where speed is crucial. Therefore, to address this challenge, a blockchain solution needs to have huge storage capacity in order to be scalable (37). As an example; this solution could be related to the development of a platform that enables the user to store PMS data that live forever on a blockchain, all while keeping high speed and a low monetary cost.

5.3. Interoperability issues – exchange of PMS data

PMS databases are off-line, centralized, local databases with a very different architecture as compared to the blockchain technology, which is distributed and decentralized. In order to implement blockchain technology, an efficient PMS database capable of enabling interoperability among the different PMS stakeholders will need to be set up (28). One of the main challenges of this implementation is that most of the global regulations still require the exchange of PMS data to be controlled by central health authorities, and they also mandate to comply with data privacy requirements when completing transactions of PMS data (27). These challenges could be mitigated with the use of a private PMS permissioned blockchain with a proof-of-authority consensus mechanism, where only a restricted number of designated and audited participants (health authorities, manufacturers and reporting facilities) have authorization to validate transactions and add them to the PMS data blockchain ledger. New global guidance need to be developed to ensure successful blockchain implementation, and that all current PMS data sources would need to be converted to the new private PMS permissioned blockchain system.

5.4. Standardization challenges

The integration of blockchain in PMS has the potential to standardize protected PMS data exchange in a more efficient manner (28). However, blockchain technology is still in its beginning, and its practical implementation in PMS of medical devices will have standardization challenges. Health Authorities should develop international standardized documents to scrutinize the shared data in terms of size, nature, and format of the data exchanged in blockchain applications. The lack of a harmonized data set could lead to each country/ region generating a block with a different data set. Blockchain applications will not deliver value if the existing PMS data exchange systems are not fully integrated, and all business rules are followed and automatically enforced.

5.5. Behavioral challenges

In addition to the mentioned technical challenges, blockchain technology is still developing, and therefore, faces behavioral challenges, like cultural change. Although the medical device industry is gradually moving toward digitization, there is still a lot that needs to be changed in order to totally transform the current heavy-administrative PMS data exchange tools to this blockchain technology, which has not yet been validated in PMS data exchange. Convincing doctors, patients, manufacturers and health authorities to switch from paperwork to making use of technology will not be an easy process and will take time and training. Due to its low adoption rate in the healthcare industry in general, the technology and regulations offered are relatively untrusted (37). The stakeholders involved in PMS process for medical devices should develop educational materials to disseminate, and identify the strengths and opportunities of blockchain technology in the medical device industry.

5.6. Monetary cost

Due to the limited talent that currently exists to write the blockchain infrastructure, it is expensive to get the data on the block, and then for a certain number of blocks to be created to ensure our block is irrevocable. Therefore, since PMS data exchange should be completed in a timely manner to ensure early identification of safety risks, we may need to speed up the transaction time (number of transactions per second). In order to do that, we may need to pay more transactional charges (which can get expensive, depending on the network availability). The cost to implement this new technology in the PMS system should be taken into consideration. Some hospitals are not fully computerized and would not be able to share data with each other (e.g. if they do not belong to the same consortium). A major shift in IT systems will need to occur and the cost of that transition to full IT systems with blockchain technology could be significant. The different PMS stakeholders (health authorities, manufacturers and hospitals) should financially support this technological shift. Some of them have already started exploring the use of this new technology; the EU Commission announced the launch of an EU Blockchain Observatory and Forum to monitor PMS data, evaluate trends, and address

Table 3. Challenges and recommendations associated with the use of blockchain technology

	Challenge	Recommendation	Owner
Security and Privacy Data	Blockchain lets the entire community, rather than a single third party, verify the records in a blockchain architecture. The PMS data becomes vulnerable to potential privacy and security risks.	Generate a private PMS permissioned blockchain with a proof-of-authority consensus mechanism.	IMDRF, HA's, Manufacturers, Hospitals
Manage data storage	Event searching and editing can be slow, which is highly unsuitable for PMS data transactions where speed is crucial.	A blockchain solution needs to have huge storage capacity in order to be scalable.	IMDRF, HA's
Interoperability issues: PMS data exchange	Current PMS databases are off-line, centralized, local databases with a very different architecture compared to blockchain, which is distributed and in the cloud.	Use of a private PMS permissioned blockchain with a proof-of-authority consensus mechanism.	IMDRF, HA's, Manufacturers, Hospitals
	Most of global regulations still require the exchange of PMS data to be controlled by central health authorities, and they also mandate to comply with data privacy requirements when completing transactions of PMS data.	Develop new global guidances to ensure blockchain implementation. All current PMS data sources converted to a blockchain system.	
Standardization challenges	PMS data exchange systems are not fully integrated.	Integration of PMS data exchange systems and development of international standardized documents to scrutinize the shared data in terms of size, nature, and format of the data exchanged in blockchain applications.	HA's, IMDRF
Behavioral challenges	Blockchain technology is still developing, and therefore, faces behavioral challenges.	Develop educational materials to disseminate, and identify the strengths and opportunities of blockchain technology in the medical device industry.	HA's, Hospitals, Manufacturers
Monetary cost	The cost of transition to full IT systems with blockchain technology could be significant.	The PMS stakeholders should financially support this technological shift.	HA's, Hospitals, Manufacturers

emerging issues (38). The project is part of an initiative to develop a standardized approach to blockchain for the EU (39) that could potentially extend to the Eudamed database in the future.

6. IMPLEMENTATION STRATEGY OF THE NEW PRIVATE PMS

DATA PERMISSIONED BLOCKCHAIN: 10-YEAR PLAN

In order to successfully implement the new private permissioned blockchain in PMS of medical devices, it is important to design a step-wise implementation strategy with clear goals, timelines, roles and responsibilities. The entire project should be funded by a consortia comprised of the different PMS stakeholders (Health Authorities, Manufacturers and Hospitals) and coordinated by IMDRF. Each member is to pay yearly fees to economically support the changes required to build and implement the new PMS system of medical devices based on the new private PMS data permissioned blockchain.

6.1. Phase I - standardization (1st – 2nd year)

The International Medical Device Regulatory Forum (IMDRF) is a group of medical device regulators (Australia – TGA, Brazil – ANVISA, Health Canada, China FDA, European Commission, Japanese PMDA and MHLW, Russian Ministry of Health, Singapore – HSA, South Korea – Ministry of Food and Drug Safety, US FDA) that have voluntarily come together to harmonize the regulatory requirements for medical products that vary from country to country. IMDRF will start a project to standardize the different PMS requirements across jurisdictions. In order to ensure that PMS data will be captured consistently in the new blockchain system, IMDRF will coordinate the standardization efforts required for the implementation of the new system. IMDRF will need to negotiate with the different PMS stakeholders (HAs, hospitals and manufacturers) to reach consensus on the identification of the PMS data sources, the adverse event reporting criteria, the adverse event coding dictionaries, and the device identification systems that will eventually be used globally in the new private permissioned blockchain.

6.2. Phase II – new global PMS database & private data permissioned blockchain (3rd – 4th year)

After agreeing and deciding on the global PMS requirements and the new global adverse event reporting dataset, IMDRF will start working with a technology partner to develop the new PMS global database software that will use a new private data permissioned blockchain with proof-of-authority to verify every PMS data transaction. Governance will need to be developed regarding participation in and the use of the new global PMS database. The principles governing transparency, confidentiality, supervision and regulatory reporting of the new database, as

well as the governing agreements of the private data permissioned blockchain will need to be agreed by all parties and documented.

6.3. Phase III – US pilot (5th year)

After agreeing and deciding on the global PMS requirements, IMDRF will start a pilot in the US for the implementation of the new private permissioned blockchain. Manufacturers will need to ensure the follow through of the use of blockchain in the supply chain management process to guarantee medical device traceability using blockchain, and convert the existing manufacturer's PMS data sources (SRS, registries ...) to blockchain. Hospitals and Health Authorities participating in the pilot will need to ensure the use of blockchain during the PMS data exchange process by converting the existing safety data sources to blockchain. The pilot should be championed by the IMDRF with the participation of one health authority (the FDA), 3 US medical device manufacturers and 3 US hospitals. The goal of this pilot will be to demonstrate blockchain's ability to connect different systems and administrations, in order to track a common dataset of product traceability and patient data, and show how blockchain could potentially improve PMS of medical devices by reducing the time it takes to alert the supply chain of a medical device recall, and reducing the time it takes to share PMS data across the different PMS stakeholders. IMDRF will need to provide a technology partner and a consulting group that will work with the manufacturers, hospitals and FDA to provide the tools, guidance and support required during the pilot. The technology partner will provide the PMS software based on the agreed standardized reporting dataset from Phase I. This software will use the blockchain infrastructure for the data transaction verification. The consulting group will support the pilot participants with training, follow-up, and most importantly will ensure that the data is well and correctly captured. Lessons learned from the pilot will be shared with all the IMDRF members.

6.4. Phase IV – global pilot (6th year)

After the successful completion of the US pilot, a second pilot will start on a global level. Again, the IMDRF should champion this second pilot, with the participation of 3 health authorities (the FDA, European Commission, China FDA), 9 medical device manufacturers (3 from US, 3 from EU, and 3 from China) and 9 hospitals (3 from US, 3 from EU, and 3 from China). The goal of this pilot will be to address unanswered questions and challenges resulted from the US pilot, and demonstrate blockchain's ability to connect different systems and administrations globally, in order to track a common dataset of product traceability and patient data, taking into consideration the different local data privacy regulations, and show how blockchain could potentially improve PMS of medical devices. IMDRF will need to provide a technology partner and a consulting group that will work with the manufacturers, hospitals and national health authorities to provide the tools, guidance and support required during the pilot. Additionally, and given the global environment, such partner and consultants

will also aid in overcoming any cultural differences associated with the implementation of this new technology (language, technological differences per country, PMS data confidentiality requirements, etc.). Lessons learned from the pilot will be shared with all the IMDRF members. If they find, at any point during or after the pilot, additional areas of focus to ensure the successful implementation globally or if any flaws or limitations are identified, the timeline of the pilot is subject to change and extension.

6.5. Phase V – new global blockchain regulations (7th – 8th year)

After the successful completion of the global pilot, each of the local health authorities coordinated by the IMDRF will develop and publish local regulations and guidelines for the local hospitals and local manufacturers to ensure successful implementation of the blockchain system by the global agreed GOLIVE date. The regulations and guidelines will contain direction on data privacy management based on the corresponding local confidentiality regulations. The documents will also include the transition period for the global implementation.

6.6. Phase VI – transition period (9th – 10th year)

During the 2-year transition period, the PMS stakeholders should work with the appropriate technological partner and consulting group (if required) to implement the GO-LIVE date. All hospitals, manufacturers and health authorities will have two years to convert the SRS and medical registries to the new private PMS data permissioned blockchain. The local health authorities will provide local technological and training support to ensure the different country PMS stakeholders will be ready to implement the new blockchain system by the agreed due date.

6.7. Phase VII – GO LIVE

After the 2-year transition period and the GO-LIVE date, a dedicated team within the IMDRF group will monitor any challenges associated with the usage of the new system. This group will provide technological and training support, when required. The local health authorities will need to enforce the use of this technology across the different local PMS stakeholders, and ensure adherence to the new private PMS data permissioned blockchain regulations during the periodic inspections of the stakeholder's PMS system.

7. CONCLUSION

Blockchain technology has great potential. Its development coincides with the timing that PMS for medical devices needs to be implemented, which offers a great opportunity and synergy. Our proposed solutions can only be successfully implemented if they are established on the basis of a solid knowledge of the current challenges and needs of the medical device industry, and in continuous collaboration with a blockchain technology expert. This expert will eliminate

the potential failure of the new system due to a lack of understanding of the performance of blockchain and its impact on PMS process. This new technology has the potential to support a more efficient approach for the PMS of medical devices, which could offer many advantages to the different stakeholders involved in the process, such as supporting new regulatory initiatives.

8. EXPERT OPINION

In order to guarantee the successful implementation of blockchain in the PMS process of medical devices, it is vital to start working on robust initiatives to address the challenges associated with the use of this new technology.

8.1. What should the PMS community focus on? prioritization

The existing resources available to the different stakeholders involved in PMS of medical devices are limited. There is a need to identify the main priorities the PMS stakeholders should focus on:

8.1.1. *Data privacy*

Blockchain provides a higher level of security as the need for a third-party involvement in the completion of the transaction of safety data is eliminated. Nevertheless, the data becomes vulnerable to potential privacy and security risks as the mechanism of blockchain allows the entire community of users, rather than a single third party, to verify the records in a blockchain architecture. PMS resources should focus on the design of solutions that ensure full data privacy to participants during the PMS data transaction, and also continue to guarantee the validation of the authenticity of the transaction.

8.1.2. *Data storage*

Contrary to the traditional centralized data storage systems, the blockchain solution offers a distributed tool to store its data. PMS is subject to large amounts of data, which must be stored on a regular basis in the blockchain and should be available to all the nodes in the chain. In order to ensure the scalability, success and availability of our blockchain, a large storage capacity will need to be provided to store all data.

8.1.3. *Data exchange*

Current PMS databases are off-line, centralized, local databases with a very different architecture as compared to the blockchain technology, which is distributed and decentralized. In order to implement blockchain technology, an efficient PMS database capable of enabling interoperability among the different PMS stakeholders will need to be set up. One of the main challenges of this implementation is that most of the global regulations still require the

exchange of PMS data to be controlled by central health authorities. New global guidances need to be developed to ensure successful blockchain implementation, and that all current PMS data sources would need to be converted to the new PMS global database software that will use the new private PMS permissioned blockchain system.

8.1.4. Data standardization

The lack of a standardized data set could lead to each country/ region generating a block with a different data set. Blockchain applications will not deliver value if the existing PMS data exchange systems are not fully integrated, and all business rules are followed and automatically enforced. International standardized documents to scrutinize the shared data in terms of size, nature, and format of the data exchanged in blockchain applications will need to be developed. If correctly implemented, blockchain technology has the potential to solve some of the current challenges associated with PMS of medical devices, and will be crucial in the future in defining the pillars of the new surveillance system.

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CHAPTER 7

**SUMMARY, GENERAL DISCUSSION AND
FUTURE PERSPECTIVES**

7.1.

**Summary, general discussion and
future perspectives**

1. SUMMARY OF FINDINGS

This thesis aims to describe the current post-market surveillance (PMS) system of medical devices, and how it may be enhanced from a technical and a regulatory perspective. We reviewed the following topics associated with PMS of medical devices: the current safety evaluation system, new PMS evaluation tools, descriptive analysis of PMS data, safety signal detection methods, and potential applications of new technologies in PMS.

Reviewing the current safety evaluation system of medical devices marked the start of our thesis (see Chapter 1). Chapter 2 compares the process and methodology used in the assessment of the safety profile of medical devices with that of medicines. The main identified gap as compared to medicines was the inconsistent collection and integration of safety information into the risk management process of medical devices. Three factors contribute to this gap; 1) lack of regulatory standardization, 2) lack of safety evaluation tools and 3) lack of risk mitigation activities targeting user error - one of the most crucial aspects related to the safety of medical devices.

In chapter 3 we performed a case study and conducted a descriptive analysis of the PMS data from one of the most important publicly available spontaneous reports database; the Food and Drug Administration's (FDA) Manufacturer and User Facility Device Experience (MAUDE) database. Our study aimed to assess the quality and quantity of spontaneous reports using MRA (metal/ceramic/ceramic/metal semi-constrained cemented or uncemented prosthesis) hip implants as a proof of concept. This case study delivered some key findings. The US was the origin of the majority of cases, and all the reports submitted to the FDA were done by manufacturers. Secondly, most reports described serious injuries; being "fracture of the hip implant" the most frequently reported event. Additionally, the reports lacked completeness and showed poor quality because the suspect medical device sample was not sent to the manufacturer and therefore could not be evaluated, which hampered root-cause analysis. Through our MRA hip implant analysis example, we identified current challenges with medical device safety surveillance. These include: Incompleteness of information in the reports, lack of specificity in regulatory reporting, lack of harmonized coding and lack of an engaged reporter who should have sent samples back for analysis.

In chapter 4, we describe the different aspects influencing the signal detection of medical devices. We identified potential gaps and outlined the challenges. In particular PMS data sources (i.e. lack of standardization of required data sets and reporting requirements across jurisdictions), signal detection methodologies (i.e. no gold standard for the methodologies used for medical device signal detection) and coding dictionaries (i.e. lack of harmonization,

consistency and granularity of event codes). To address those concerns, we recommended the following:

- The use of a distributed safety data system and the global standardization of regulatory reporting and the development of common data collection elements to avoid different levels of completeness in individual device cases. This new common standardized data set should be adopted by the different stakeholders involved in the process of collection and extraction of safety data for signal detection purposes.
- Development of guidance on gold standard methodologies to mine data from the different types of PMS data sources.
- Use of the International Medical Device Regulators Forum (IMDRF) coding dictionary as gold standard to be used by the different PMS stakeholders. The IMDRF team should develop coding guidelines classified by therapeutic area, and additional IMDRF codes to increase granularity, when appropriate.
- The Unique Device Identifier (UDI) system will also need to be fully implemented to be able to link the different safety data sources.

In chapter 5, we describe the new EU regulatory requirements in PMS, to compare it with existing experience in medicinal products and to provide recommendations for the implementation of the PMS plan. The authors propose a PMS plan template that should consist of a PMS plan Core and a PMS plan Supplement. The PMS plan Core document will describe the manufacturer's general PMS system and the PMS plan Supplement will define the specific PMS activities performed by the manufacturer for a particular medical device or family/group of medical devices. The PMS plan should have clear objectives, a predefined structure with specifications on data integrity, periodicity, and defined responsibilities. The authors recommend a modular structure of the PMS plan contents, to facilitate consistent updating of PMS information. To deliver high-quality PMS plans, companies need to implement a system that includes cross-functional reviews and patient and customer feedback. To ensure the successful implementation of the PMS plan, the authors propose different KPIs. These indicators will help measure the effectiveness of the plan.

In chapter 6, we explored the different technical aspects of blockchain and how this new technology can support the ongoing efforts to improve the PMS system for medical devices. The private PMS blockchain for medical devices might impact the different stakeholders involved in the PMS data exchange process, by enhancing efficiency in PMS data exchange, and the management of PMS data. Using blockchain in safety data exchange could decrease safety data processing time. Once a patient enrolls in a study, registry or reports a complaint, a complete collection of data becomes readily available due to the availability of data on the distributed ledger. Additionally, surgeons, manufacturers and health authorities would have access to original, and quality source-documented data in real time; decreasing the likelihood

of incorrect data regarding the patient's medical history. This could strengthen the trust in the safety evaluation system for medical devices. New technologies such as blockchain are part of a new era and have the potential to lead to the establishment of a more proactive PMS system that could allow real time identification of safety issues, if well implemented.

Chapter 7 contains a summary of the findings from this thesis, a general discussion around the implications of these findings and recommendations for current regulatory practices and future research.

2. GENERAL DISCUSSION AND FUTURE PERSPECTIVES

2.1. The need for change

Recent public health safety scandals involving medical devices have emphasized that PMS is vital to monitor the safety of all medical devices that enter the market. Following several scandals, there has been a growing demand for the improvement of the current passive-reactive system of medical device safety monitoring, so that public health safety issues like the metal-on-metal hip implant scandal do not reoccur and are avoided all together in the future. Different global regulatory initiatives have supported this change and aim to create a new, more transparent, efficient and proactive medical device PMS system (1).

The aim of this thesis is to present a comprehensive overview of the current PMS system for medical devices, and to explore how such a system may be enhanced from a technical and a regulatory perspective, taking into consideration the many complex interdependent factors that contribute to adverse events.

2.2. Seizing the opportunities presented by change

In the case of safety surveillance of medical devices, the need for change arose due to the failure of the current reactive safety surveillance system, which is not fit for purpose as it has not always effectively protected the patient. The main goal of the safety surveillance system should be the optimization of public health and the protection of the patient by identifying potential safety issues associated with medical devices in a timely and effective manner.

The new PMS system (figure 1) should consist of a real time PMS data (SRS, PMCF studies, device registries) collection process preferably using Blockchain Technology (BT) for traceability followed by an automated upload into the global decentralized safety database through Robotic Process Automation (RPA). Coding should be done using automated adverse event/technical complaint coding via Machine Learning (ML). Medical review should be conducted

to evaluate concerns. In the safety database, statistical signal detection and corresponding signal validation, might be conducted, to identify safety signals associated with the use of the medical device. After the signal validation process, escalation of a safety signal may be considered.

If the safety issue is escalated, a market action using BT for device traceability, or educational risk minimization activities -such as user training via Augmented Reality (AR) / Virtual Reality (VR)- may be necessary. The data gathered during PMS is evaluated during the life cycle management review process. The conclusions of this evaluation may lead to the update of medical device design records, risk management documents, clinical evaluation reports or the marketing strategy. The ultimate goal of this new system is to ensure that the decisions by regulatory agencies, healthcare professionals and manufacturers are grounded in science.

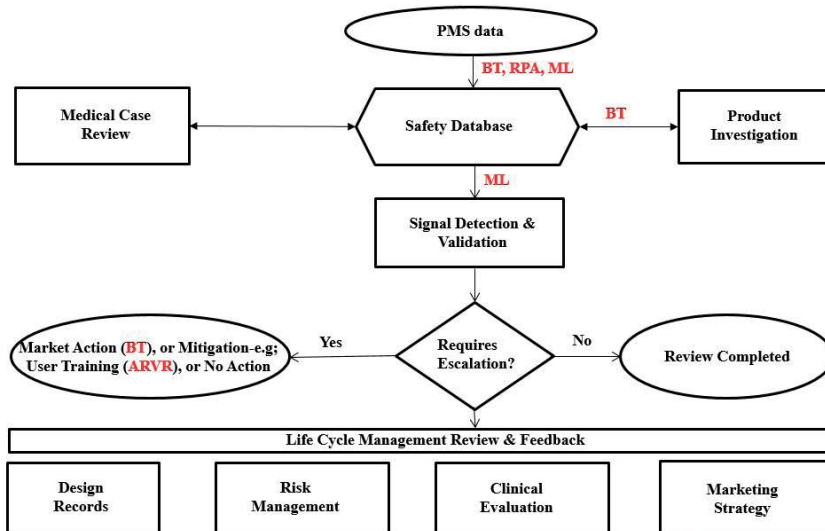


Figure 1. New PMS system: process map

2.3. New tools and technological solutions to support the new PMS system

New tools and technological solutions will need to support the implementation of the new PMS system. We proposed a PMS plan template that should consist of a Core and a Supplement. The PMS plan Core document should describe the manufacturer’s general PMS system and the PMS plan Supplement should define the specific PMS activities performed by the manufacturer for a particular medical device or family/group of medical devices. The PMS plan should have clear objectives, a robust structure with specifications on data integrity, periodicity, and defined responsibilities. We recommend a modular structure of the PMS plan to facilitate consistent updating of PMS information, similar to that of medicinal products. To deliver

high-quality PMS plans, companies need to implement a system that includes cross-functional reviews and patient feedback. To evaluate the PMS plan, we propose use of different Key Performance Indicators (KPIs).

New technological solutions may support the implementation of the new system. In chapter 6, we explored the different technical aspects of blockchain and how this new technology may support the ongoing efforts to improve the PMS system for medical devices. The private PMS blockchain for medical devices could impact the different stakeholders involved in the PMS data exchange process, by enhancing efficiency in PMS data exchange, and the management of PMS data. Using blockchain in safety data exchange could decrease safety data processing time. Once a patient enrolls in a study, registry or reports a complaint, a complete collection of data becomes readily available due to the availability of data on the distributed ledger. Additionally, surgeons, manufacturers and health authorities would have access to original, and quality source-documented data in real time; allowing for improvement of correct data regarding the patient’s medical history.

2.4. Recommendations

Following the identification of multiple areas for improvement in the processes associated with medical devices PMS, we made different recommendations to address the identified challenges. We also identified the key aspects required to build the new PMS system for medical devices which is described in figure 2:

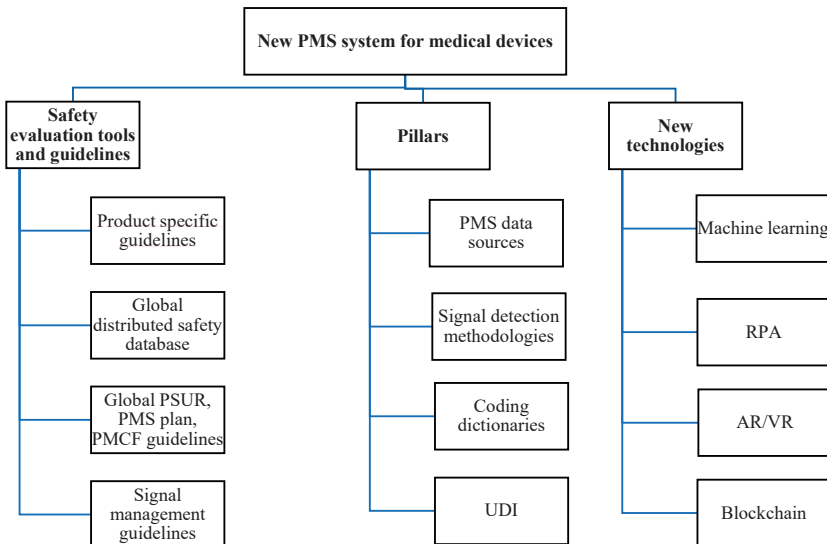


Figure 2. Key aspects to build the new PMS system for medical devices
 Abbreviations: PSUR, Periodic Safety Update Report; PMS, Post-Market Surveillance; PMCF, Post-Market Surveillance; UDI, Unique Device Identifier; RPA, Robotic Process Automation; AR/VR, Augmented Reality / Virtual Reality

2.4.1. Safety evaluation: Develop and expand the use of new tools and guidelines

Relevant authorities should make more safety evaluation tools and provide an adequate infrastructure to improve medical device safety assessment. Suggested infrastructure and tools would be the following;

- **Regulatory documents providing further guidance** on the different steps in the signal management process, similar to the signal detection guidance for medicines: the report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group VIII and the guidelines on good pharmacovigilance practices (GVP) module IX—signal management (2).
- A **global distributed medical device safety database**
- A **global PMS (PMS) plan** should be submitted for every medical device or group of medical devices to serve as a summary of all collected post-market information and as a guide to utilizing such information (1).
 - o **Global PSURs** for every medical device or family of medical devices to strengthen the benefit–risk analysis (1).
 - o A **post-market clinical follow-up study plan** should also be part of the PMS plan and be developed with the results of initial trials in mind (1)
- Guidance about required **clinical data** (from both a quantitative and a qualitative perspective) to obtain the market approval should be defined in guidelines and should be consistent with the risk associated with the product and/or how innovative the device is. Medical devices with a high level of innovation (new material, new product, new surgical procedure) and/or a high level of risk should require more clinical data. For these types of products, more evidence should be generated during the pre-market phase to better define expected risks. Randomized controlled trials (RCTs) with these types of implantable medical devices should be conducted when required and possible. Previous experience with similar devices should also be considered as evidence when deciding which clinical data are required (3).

2.4.2. PMS pillars: Standardization and harmonization of PMS processes

2.4.2.1. PMS data sources

The data available before licensing of a medical device is limited and ‘real-world’ data obtained from PMS data sources will add significant value to the knowledge of the medical devices safety profile (3). There are different types of PMS data that can be used for signaling purposes. The main ones are: spontaneous reporting databases, post-market clinical follow-up studies (PMCF), electronic health records (EHRs) and medical device registries. Passive surveillance based on spontaneous reporting to the health agencies is already a legal requirement and not further described in detail in this paragraph (1). Active surveillance systems such as Medical

Device registries present additional opportunities for medical device-related outcomes data and information regarding the denominator. Safety data from medical device registries can provide information on the performance of a device in actual clinical care and allow to identify risks and complications that have not been characterized during pre-market clinical investigations. Registries have the potential to provide valuable information to the different PMS stakeholders such as medical device manufacturers, health care professionals, patients and health agencies. Collaboration between these stakeholders is key for the development and expansion of registries (5).

It is recommended that the International Medical Device Regulators Forum (IMDRF) leads and promotes the harmonization of national medical device registry databases. IMDRF is a group of medical device regulators (Australia, Brazil, Canada, China, Europe, Japan, Russia, Singapore, South Korea, and the United States of America) who have come together to build on the strong foundational work of the Global Harmonization Task Force (GHTF) on Medical Devices and aims to accelerate international medical device regulatory harmonization and convergence. This harmonization could be established by using the international Coordinated Registry Network (iCRNs) to maximize the potential of information collected in the international registries (6). iCRNs are a key Medical Device Epidemiology Network (MDEpiNet) strategy to bring together real-world data from a variety of sources to address the needs of device safety evaluation for various stakeholders. One of the iCRN, the International Consortium of Orthopedic Registries (ICOR), serves an excellent example of the use of a distributed safety data system with harmonized data definitions and data extraction followed by evaluating the data using innovative methodology across multiple national orthopedic registries. This decentralized structure system helps to overcome challenges related to security, operations, legal, and patient privacy (7). In order to connect the different data received from the PMS data sources (SRS or registries), it is also recommended that guidance on common data elements and common standardized data sets for reporting of individual device cases are developed (both for SRS and registries). This guidance should be adopted by the different stakeholders involved in the process of collection and extraction of safety data for signal detection purposes.

Finally, we recommend the development of a global decentralized safety database that includes safety data reported from different PMS data sources (SRS, PMCF studies, EHRs and medical device registries).

2.4.2.2. Signal detection methodologies

At this time there is no agreement about quantitative signal detection methods for medical devices for each of the different PMS data sources (SRS, registries and nonstandard data sources) exists, and no gold standard has yet been established. IMDRF and Health Authorities

should work together to develop guidance on gold standard methodologies used to mine data from the different types of PMS data sources.

2.4.2.3. Coding dictionaries

Different coding dictionaries are currently used for recording safety concerns with medical devices. In order to create a signal detection system that evaluates global PMS data, a standardized coding dictionary should be available to describe patient harm, the product problem and evaluation (8). We recommend the adoption of the IMDRF coding dictionary (figure 3) by all Global Health Authorities.

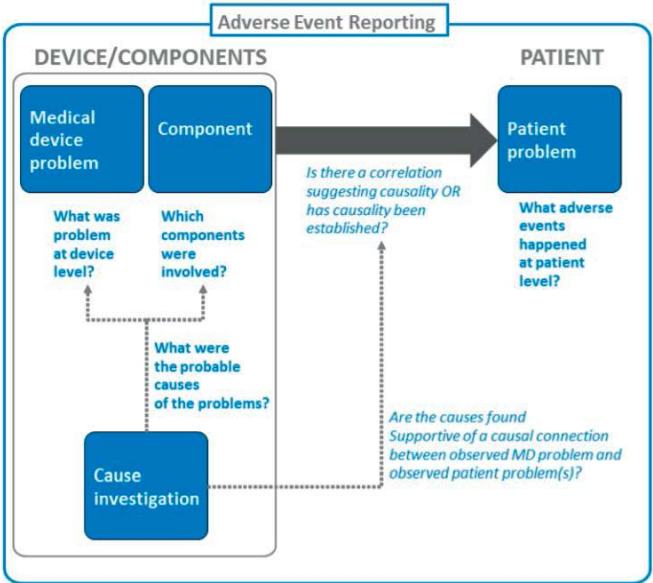


Figure 3. The Adverse Event Reporting terminology is composed of four sets of terminologies: 1-Medical device problem terminology, 2-Components terminology, 3- Cause investigation terminology and 4-Health Effects terminology (9).

Note that for an effective monitoring of adverse events, means of effectively identifying devices as well as the category they belong to (e.g. GMDN) are important.

The existing coding dictionaries will need to mirror the IMDRF coding dictionary to allow for an efficient system to exchange signal detection of medical devices. Taking into consideration that IMDRF codes are very high level with many events falling in the “no code available” category, and in order to ensure consistency when selecting the appropriate codes, we also recommend elaborating on the coding to add granularity, and the development of IMDRF coding guidelines classified by therapeutic area. IMDRF needs to ensure maintenance of the coding dictionary, and develop additional codes to increase specificity/granularity.

2.4.2.4. Unique Device Identification

To ensure successful implementation of the global PMS system for medical devices, a global harmonized system for Unique Device Identifiers (UDIs) needs to be implemented. The UDIs need to be consistently assembled within the different PMS data, and all stakeholders need to ensure a continual use of the SRS and registries, together with UDIs. The full implementation of the UDI will allow the identification and traceability of the medical device throughout its life cycle, and also link the different data sources.

The identification of devices during the signal detection process will continue to be a hurdle until the UDI is standardized and widely utilized for some time. This is a long-term goal as it involves significant policy changes. For these recommendations to succeed, all stakeholders must actively collaborate and support each other.

2.4.3. New technologies as the cornerstone of the new surveillance system

The size of objective evidence available to be analyzed under a medical device PMS system will grow exponentially in the future. One of the main goals of the new regulations is to ensure a rapid, reliable and efficient exchange of safety data to ensure that medical device safety issues are identified in a timely manner, and appropriate action is taken. Proactive approaches to PMS processes become more important as regulators increase the scrutiny of device safety (1, 4). This changing regulatory environment has led many of the medical device safety surveillance stakeholders to explore solutions to address the associated challenges. We suggest that stakeholders should focus on new technological solutions that could support the creation of the new medical device PMS system (see figure 2). Some of the solutions that have been explored thus far in the area of medical devices include:

2.4.3.1. Machine Learning

Machine learning (ML) refers to methods that have the ability to learn, train, validate and examine the data in order to provide meaningful outputs. In the world of PMS of medical devices, machine learning algorithms can be developed and trained using the global safety database fields for annotation of complaint source documents (10). Machine learning methods can also complement traditional analytic methods for medical device surveillance; for example the event code selection based on adverse event narratives or the safety signal detection process of medical device registries (11).

2.4.3.2. Robotic Process Automation

Another automated intelligence solution is the Robotic Process Automation (RPA). RPA uses robots that mirror human activity on existing systems and applications to do repetitive and time-consuming activities. An example of this new technology is the automation of the

processing of Case Reports submitted by consumers, healthcare professionals or regulators into the manufacturer's complaint database (12).

2.4.3.3. Augmented Reality and Virtual Reality

Augmented Reality (AR) and Virtual Reality (VR) are technologies that challenge the separation between the real and virtual world and introduce new opportunities to the PMS system for medical devices. AR is an interactive experience of a real-world environment where real world objects are enhanced with computer-generated perceptual information. VR is a complete immersive virtual experience, formed using only real-world content, only artificial content or a combination of both.

In the medical device world, AR/VR can support the user of medical devices by reducing the user learning curve to implant new medical devices. VR brings an interactive experience to the medical device user (surgeon, nurse, pharmacist, etc) by simulating real world situations, such as a new medical device being used by the healthcare professional during surgery. For example; through the use of AR, the surgeon is able to upload and use virtual ultrasound images on the patient while performing surgery (13).

2.4.3.4. Blockchain

At present, blockchain is mainly used to verify transactions within digital currencies. A blockchain user may also use the technology to digitize, code and insert virtually any transaction of information in an immutable, distributed and secure manner. We propose a private PMS blockchain for medical devices that could potentially bring significant enhancements by improving efficiency in PMS data exchange, and management. Using blockchain in the safety data environment would reduce safety data handling time and has the potential to support medical device product investigation and related market actions by strengthening device traceability.

Our recommendation is to start leveraging these technologies to support the implementation of the new system.

2.5. Possible future challenges and proposed solutions

2.5.1. Security and data privacy

The proposed PMS system will grant the entire PMS community access to a great amount of PMS data; SRS, registries, non-standard PMS data sources. However, such sensitive patient level data is subjected to potential privacy and security regulations. A private PMS permissioned blockchain with a proof-of-authority consensus mechanism, where only a restricted number of designated and audited participants have authorization to validate transactions and add them to the PMS data blockchain ledger may support this.

2.5.2. Standardization of efforts

The proposed PMS system will not deliver value if the existing PMS data exchange systems are not fully integrated and standardized, and all business rules are followed and automatically enforced.

The biggest challenge lies in the creation of a mutual beneficial and agreeable standardized system, that all stakeholders feel comfortable working and engaging with.

Adequate global guidelines, and corresponding training should be in place to ensure all PMS stakeholders understand the importance and the need for standardization and act accordingly. IMDRF should lead the standardization efforts taking into consideration the different interests of all PMS stakeholders.

2.5.3. Behavioral barriers

The new requirements associated with this system will need to be adopted by all the members of the PMS community. A high level of transparency and accountability is the cornerstone of success of the new system. The implementation of this new system may be exposed to behavioral barriers that could result from stakeholders being reluctant to share their safety data.

In order to promote transparency and accountability associated with the use of this new system, the PMS community should develop educational materials to disseminate, and identify the strengths and opportunities of this new system. A particularly needed target are the healthcare professionals who leave Medical Schools in many countries without basic notions of pharmacovigilance and even less understanding of medical device vigilance.

2.5.4. Monetary cost of technological shift

A major technology shift will need to be completed by the PMS community, and the cost of this transition could be significant. Some medical device manufacturers or hospitals may not have the financial and technological infrastructure to support this change. Thorough Return On Investment (ROI) reports should be developed by the medical device manufacturers taking into consideration not only the safety benefits associated with the new system (timely detection of safety issues, and compliance with reporting requirements), but also the different business benefits associated with this technological change such as:

- Real time customer/patient feedback: the new system will provide real time feedback on potential safety issues to the manufacturers, and the ability to improve customer experience, and increase customer satisfaction via the reduction of adverse events.
- Increased productivity: this technological shift will allow employees to do more work in less time, and eliminate some of the redundancies that exist in the current PMS system. For example, in the current system the same safety data entry process is being completed

each time a new PMS stakeholder (Hospital, Manufacturer, Health Authority) receives new safety data. In the new PMS system, the safety data entry step will be performed only once eliminating this duplicate step across the PMS process.

- **Lower costs:** This change could potentially reduce expenses for manufacturers. The maintenance cost of the shared global distributed safety database would be split amongst all stakeholders, and possibly lower current expense levels. This system will ultimately lead to faster detection of safety issues which would then reduce hospitalizations and lifetime disabilities resulting in lower costs for social security.

Medical device manufacturers or hospitals, who will not have the means to financially fund this technological shift should be economically supported by their local HAs.

2.6. Implementation plan of the new safety surveillance system

In order to successfully implement the new safety surveillance system of medical devices, it is important to design a step-wise implementation strategy with clear goals, timelines, roles and responsibilities. The entire project should be funded by a consortia comprised of the different stakeholders involved in the safety surveillance (Health Authorities, Manufacturers, Hospitals) and coordinated by IMDRF. Suggested timelines are as following:

- **Phase I- Standardization (1st – 2nd year):** IMDRF should commence a project to standardize the different PMS requirements across jurisdictions.
- **Phase II – New global safety database (3rd – 4th year):** IMDRF should work with a technology partner to develop the new global safety database software.
- **Phase III – US Pilot (5th year):** The pilot should be championed by the IMDRF with the participation of one health authority (the FDA), 3 US medical device manufacturers and 3 US hospitals. The goal of this pilot should be to demonstrate the system's ability to timely identify safety issues.
- **Phase IV – Global Pilot (6th year):** The IMDRF should champion this second pilot, with the participation of 3 health authorities (the FDA, European Commission, China FDA), 9 medical device manufacturers (3 from US, 3 from EU, and 3 from China) and 9 hospitals (3 from US, 3 from EU, and 3 from China). The goal of this pilot should be to address pending questions and challenges resulting from the US pilot.
- **Phase V – New global regulations related to the new safety surveillance system (7th – 8th year):** Each of the local health authorities coordinated by the IMDRF should develop and publish local regulations and guidelines for the local hospitals and local manufacturers to ensure successful implementation of the new safety surveillance system.
- **Phase VI – Transition period (9th – 10th year):** During the 2-year transition period, the PMS stakeholders should work to implement the new surveillance system.

- **Phase VII – GO LIVE:** After the 2-year transition period and the GO-LIVE date, a dedicated team within the IMDRF group should monitor any challenges associated with the usage of the new system.

2.6. Conclusion

The driving force behind exploring PMS of medical devices and its related processes is the need for earlier detection of safety issues, and hence, earlier management of potential safety issues. This thesis aimed to analyze the current state of the PMS system and provides recommendations on how to improve the system from a technical and regulatory perspective. Despite the challenges associated with the current system, PMS stakeholders have the opportunity to change the landscape of safety surveillance of medical devices by taking advantage of new technologies to harmonize and standardize current processes, and expand the scope of the current surveillance approach by leveraging new PMS data sources to support evidence-based regulatory decision making.

A notable shift towards an increased usage of proactive safety data sources has recently started in the field of PMS of medical devices; medical device registries have the potential to increase heterogeneity and size of available populations for safety evaluation of medical devices, at a level that cannot be achieved by SRS databases alone (5). New safety evaluation tools, like the PMS plans, have the potential to serve as a thorough instrument to describe the benefit-risk evaluation of medical devices. Such plan will be a key part in the establishment of the new framework for the proactive safety evaluation of medical devices.

In conclusion, there is a need for regulatory and technical standardization that, together with the creation of big PMS distributed data networks, will support the early detection of potential safety issues associated with medical devices.

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7.2.

Nederlandse samenvatting

Dit proefschrift heeft als doel de post-market surveillance (PMS) van medische hulpmiddelen te beschrijven en te onderzoeken hoe dit kan worden verbeterd vanuit technisch en regelgevend perspectief.

De volgende onderwerpen komen in deze thesis aan bod: het huidige PMS systeem voor de veiligheid van medische hulpmiddelen, de ontwikkeling van nieuwe PMS-evaluatie methodes, een beschrijvende analyse van PMS-data, bespreking van de methodes voor het identificeren van signalen en mogelijke toepassingen van nieuwe technologieën in de PMS van medische hulpmiddelen. De indeling van het proefschrift is als volgt:

In *hoofdstuk 1* beschrijven we het huidige PMS-systeem voor medische hulpmiddelen. In *hoofdstuk 2* bespreken we de processen en de methodologie die worden gebruikt bij de beoordeling van de veiligheid van medische hulpmiddelen en vergelijken we die met de methodes gebruikt bij de PMS van geneesmiddelen. De belangrijkste tekortkoming in de PMS van medische hulpmiddelen - t.o.v. het bestaande systeem voor geneesmiddelen - is het gebrek aan consistentie niet alleen wat betreft de dataverzameling op zich, maar ook wat betreft de integratie van nieuwe gegevens bij het risicobeheerproces van medische hulpmiddelen. Drie factoren dragen hieraan bij: 1) gebrek aan een eenduidige wetgeving rond medische hulpmiddelen, 2) onvoldoende methodes gericht op de PMS van medische hulpmiddelen en 3) een gebrek aan risicobeperkende activiteiten gericht op de preventie van fouten bij het gebruik van een medisch hulpmiddel - één van de meest cruciale aspecten van de veiligheid van medische hulpmiddelen.

In *hoofdstuk 3* worden de resultaten van een *case study* besproken, gebruik makend van PMS-data van de Manufacturer and User Facility Device Experience (MAUDE) database van de Food and Drug Administration (FDA). Dit onderzoek was gericht op het beoordelen van de kwaliteit en kwantiteit van spontane meldingen gerelateerd aan heupprothesen (product code MRA). Deze studie leverde een aantal belangrijke resultaten op. Ten eerste kwamen de meeste meldingen uit de Verenigde Staten (VS) en werden de meeste meldingen door de fabrikant zelf gerapporteerd. Ten tweede beschreven de meeste rapporten ernstige problemen waarbij “breuk van het heupimplantaat” het vaakst gerapporteerd werd. Bovendien waren de rapporten vaak niet volledig en van lage kwaliteit gezien verdachte hulpmiddelen niet naar de fabrikant werden gestuurd voor “*root-cause*” analyse. De resultaten van deze studie tonen de knelpunten rond PMS van medische hulpmiddelen. Die knelpunten zijn de volgende: onvolledige rapporten, onvoldoende regelgeving rond het rapporteren van spontane meldingen van medische hulpmiddelen, gebrek aan harmonisatie in gebruikte codering en onvoldoende bereidheid om medische hulpmiddelen naar de fabrikant te sturen voor verdere analyse.

In *hoofdstuk 4* beschrijven we - aan de hand van een literatuurstudie - de verschillende aspecten die belangrijk zijn bij de signaaldetectie van medische hulpmiddelen. Deze studie liet ons toe de huidige problemen en uitdagingen in kaart te brengen, met nadruk op het volgende: tekort aan standaardisatie van datasets en rapportagevereisten over verscheidene jurisdicties, afwezigheid van een gouden standaard wat betreft de methodologie voor het identificeren van potentiële signalen rond medische hulpmiddelen en onvoldoende harmonisatie, consistentie en granulariteit bij de codering van bijwerkingen. Om deze beperkingen aan te pakken, adviseren we het volgende:

- Het gebruik van een gedistribueerd systeem voor het opvolgen van de PMS van medische hulpmiddelen en een gestandaardiseerde globale aanpak voor zowel regelgeving als dataverzameling wat moet leiden tot een nieuw en gestandaardiseerd dataset.
- Ontwikkeling van richtlijnen rond de keuze voor methodes bij signaaldetectie van PMS-data van medische hulpmiddelen.
- Het standaard gebruiken van het “International Medical Device Regulators Forum (IMDRF)” coderingswoordenboek door alle partners betrokken bij de veiligheid van medische hulpmiddelen. Hieraan gerelateerd is verdere ontwikkeling van het IMDRF aangewezen om de granulariteit te vergroten.
- Het gebruik van het Unique Device Identifier (UDI)-systeem wat unieke koppeling tussen verschillende bronnen mogelijk maakt.

In *hoofdstuk 5* beschrijven we de nieuwe regulatoire eisen van de Europese Unie (EU) wat betreft PMS en gaan we na of het bestaande PMS-plan voor geneesmiddelen ook kan geïmplementeerd worden voor medische hulpmiddelen. Wij adviseren dat het PMS-plan voor medische hulpmiddelen zou bestaan uit een kerndocument en een supplement. Het kerndocument beschrijft het algemene PMS-systeem van de fabrikant terwijl het supplement de product-specifieke PMS-activiteiten beschrijft. Het PMS-plan moet duidelijke doelstellingen schetsen en specificaties omvatten rond gegevensintegriteit, periodiciteit en verantwoordelijkheden. Idealiter wordt het PMS-plan modulair opgebouwd wat latere aanvullingen van het plan vereenvoudigt. Om de kwaliteit van de PMS-plannen te optimaliseren is het noodzakelijk dat zowel patiënten als zorgpersoneel feedback kunnen geven. Het gebruik van Key Performance Indicators (KPIs) zal helpen om de doeltreffendheid van het PMS-plan te kwantificeren.

Hoofdstuk 6 staat stil bij het principe van “*blockchain*” en gaat na of deze nieuwe technologie een bijdrage kan leveren aan het optimaliseren van de PMS van medische hulpmiddelen. Het gebruik van de blockchain methodologie heeft als voordeel dat het de tijd voor uitwisseling van data aanzienlijk kan verkorten. Zodra een patiënt toestemming geeft tot deelname aan een klinische studie, zich inschrijft in een patiënten-register of een bijwerking rapporteert, zijn de gegevens van die patiënt centraal beschikbaar en is het exacte tijdstip van het delen van deze informatie gedocumenteerd. De blockchain technologie laat toe dat artsen, fabrikanten en

regelgevende gezondheidsautoriteiten in ‘realtime’ toegang hebben tot de geanonimiseerde gegevens die nodig zijn voor het beoordelen van de spontane meldingen. Nieuwe technologieën zoals blockchain kunnen leiden tot een proactief PMS-systeem dat, indien goed geïmplementeerd, het snel identificeren van (nieuwe) signalen mogelijk maakt.

Hoofdstuk 7 omvat de samenvatting van dit proefschrift alsook een algemene discussie waarin we toelichting geven over de implicaties van onze bevindingen, aanbevelingen maken over de bestaande wetgeving en suggesties doen voor toekomstig onderzoek.

CHAPTER 8

List of publications

- **Pane J.**, Coloma P.M., Verhamme K.M.C., Sturkenboom M.C.J.M., Rebollo I. Evaluating the Safety Profile of Non-Active Implantable Medical Devices. *Drug Saf.* 2017. 40: 37. doi:10.1007/s40264-016-0474-1.
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CHAPTER 9

PhD portfolio

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2014-2019 FDA Vigilance Medical Device Regulation Training. Alcon (Novartis). Fort Worth (USA).

2014-2019 EU Vigilance Reporting Requirements Training. Alcon (Novartis). Fort Worth (USA).

2017: D4M2: Substantiation and Quantification of Risks. Eu2P programme. Erasmus Medical Center University of Rotterdam (Netherlands).

2017: Pre-Approval Safety Requirements for Medical Devices. Alcon (Novartis). Fort Worth (USA).

2017: Post-marketing Safety Requirements for Medical Devices. Alcon (Novartis). Fort Worth (USA).

2017: Medical Devices Case Processing. Alcon (Novartis). Fort Worth (USA).

2017: Project Management Fundamentals. Alcon (Novartis). Fort Worth (USA).

2018: Operational excellence in Patient Safety & Pharmacovigilance. Alcon (Novartis). Fort Worth (USA).

2019: Blockchain Overview. Smart Kx. Dallas (USA).

2020: Clinical and Safety Training under the EU Medical Device Regulation 2017/745. Alcon. Fort Worth (USA).

Oral presentations

2014-2015. Global Safety Database Alcon (Novartis). Barcelona (Spain).

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2015-2019. Post-market Surveillance & Vigilance. Alcon (Novartis). Fort Worth (USA).

International conferences

2014-2015: EUCOMED (MedTech Europe); Post-market Surveillance Working group – meetings. Brussels (Belgium).

2014-2015: Basics on Post-market Surveillance. Alcon (Novartis). Barcelona (Spain).

2015: Post-market Surveillance and Vigilance. Informa. Amsterdam (Netherlands).

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Peer reviewer

2019 Drug Safety.

2019-2020 Pharmacoepidemiology and Drug Safety.

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2021 Methods of Information in Medicine.

2021 Medical Devices: Evidence and Research.

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CHAPTER 10

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CHAPTER 11

About the author

Josep M. Pané grew up in Barcelona, Catalonia (Spain), and is a graduate of Pare Manyanet High School. In 2004, Josep started his pharmaceutical studies at the school of Pharmacy at the University of Barcelona. Consequently, he obtained his Pharmacy degree in 2009.



His university years working part-time as a pharmacist in a community pharmacy, and as a research assistant in the University Pharmaceutical Technology department led to Josep's strong interest in patient safety and in the pharmaceutical industry. Following his first degree in Pharmacy, he started working in Alcon (Novartis)'s Medical Safety department. In 2009, after having joined the pharmaceutical industry, Josep further wanted to strengthen his educational background and started a part-time Masters in Pharmaceutical Industry at the Center for Advanced Studies in the Pharmaceutical Industry (CESIF) in Barcelona, which he successfully completed in autumn 2010.

In 2013, Josep completed a second advanced degree, his Master of Science in Pharmacology. With the knowledge he gained throughout the initial industry experience, Josep recognized a gap in the framework of the overall safety surveillance process for medical devices, which ultimately led to his decision to pursue a PhD. After presenting his proposed research topic to the EU2P PhD doctoral board, Josep was selected as one of the EU2P PhD candidates, and was assigned Erasmus Medical Center University of Rotterdam (Netherlands) as his PhD institution. In 2014, Josep started working on his PhD, with a focus on safety surveillance of medical devices. He continued to work in Alcon (Novartis)'s Medical Safety department.

From 2013 through 2015, Josep also worked as a lecturer at the University of Barcelona IL-3 post-graduate program teaching Safety Surveillance of Medical Devices. During his PhD research, he has too collaborated as peer reviewer with the official journal of the International Society of Pharmacovigilance (ISoP); Drug Safety, with the official journal of the International Society of Pharmacoepidemiology (ISPE); Pharmacoepidemiology and Drug Safety, Methods of Information in Medicine journal, Medical Devices Evidence & Research journal, and with Expert Review of Medical Devices journal. In 2015, after six years in the Medical Safety's regional office in Barcelona, Josep was promoted to Alcon's Headquarters in Fort Worth, Texas (USA), where he continued his industry career working in different capacities of successively increasing responsibility until he accepted an opportunity with UCB Pharma in the Global Medical Device Safety and Vigilance team, and relocated back to Europe in April 2021. Josep has strong expertise in designing and implementing safety evaluation processes. His past achievements include building high-performing teams and leading cross-functional groups for execution of global projects.

In his spare time, Josep is an advocate of team handball; a sport he has been playing since his childhood. Josep enjoys spending time with his wife Patricia, family and friends. Josep is interested in history, politics and learning about new technologies.

