EVALUATING THE IMPACT OF SAFETY NOTICES ON KNEE IMPLANT UTILIZATION: A SOCIO-TECHNICAL ANALYSIS

By

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Do not go gentle into that good night,
Old age should burn and rave at close of day;
Rage, rage against the dying of the light.

Though wise men at their end know dark is right,
Because their words had forked no lightning they
Do not go gentle into that good night.

Good men, the last wave by, crying how bright
Their frail deeds might have danced in a green bay,
Rage, rage against the dying of the light.

Wild men who caught and sang the sun in flight,
And learn, too late, they grieved it on its way,
Do not go gentle into that good night.

Grave men, near death, who see with blinding sight
Blind eyes could blaze like meteors and be gay,
Rage, rage against the dying of the light.

And you, my father, there on the sad height,
Curse, bless, me now with your fierce tears, I pray.
Do not go gentle into that good night.
Rage, rage against the dying of the light.

-Dylan Thomas, Do not go gentle into that good night

ABSTRACT

This thesis examines the effects of safety notices on the utilization of knee implants in orthopedic practices. Utilizing a blend of correlation analysis, machine learning techniques, and interrupted time series analysis, this study evaluates the impact of safety notices on the market share of diverse knee implant models. The analysis leverages a dataset comprising safety notices, market share figures, and analytical model outputs to investigate both the direct and indirect influences of these notices on clinical decision-making processes.

Although safety notices are integral to regulatory compliance and patient safety under the Medical Device Regulation (MDR), which mandates continuous monitoring of device performance, findings indicate that these notices seldom significantly alter clinical practices or market shares. Notable exceptions include specific models such as Advance, Evolution, and Journey, which display variable impacts, suggesting the presence of other complex factors at play in clinical decision-making. These findings illustrate the complex dynamics of clinical responses to regulatory initiatives and underscore the need for more robust monitoring and evaluation strategies to determine the effectiveness of safety notices in post-market surveillance.

The thesis underscores the need to enhance post-market surveillance systems to more accurately assess the influence of safety notices on clinical practice, thereby addressing a crucial knowledge gap. By recommending directions for future research aimed at elucidating the subtle effects of safety notices, this work strives to maximize their utility and foster improved outcomes in patient care within the realm of medical devices. This research establishes a foundation for understanding the practical implications of safety notices in clinical environments, ensuring that regulatory measures are more closely aligned with clinical requirements, which will be useful for future research.

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Chapter 1

1.1 Research Problem Introduction

Total Knee Arthroplasty (TKA) is a surgical intervention designed to alleviate pain and restore mobility in patients suffering from advanced joint disease or deterioration. Despite advancements in knee implant technology, approximately 20% of patients continue to experience dissatisfaction, with ongoing issues such as persistent pain, functional limitations, and unmet expectations regarding implant longevity (Kahlenberg et al., 2019). These outcomes suggest that, while technological improvements have been made, significant challenges remain in achieving optimal patient satisfaction and long-term success of these implants.

One of the aspects of ensuring the safety and effectiveness of knee implants is robust post-market surveillance. This process involves continuous monitoring of medical devices once they are in widespread clinical use, aiming to identify and mitigate risks that were not apparent during pre-market evaluation. Instances such as the high failure rates observed in the Optetrak (Exactech) knee implants, which were initially successful but later exhibited problems after changes in the packaging process, underscore the importance of vigilant post-market monitoring (Food and Drug Administration, 2023). Such incidents highlight the need for mechanisms to inform and guide clinical practices, ensuring that both healthcare providers and patients are adequately aware of potential risks associated with these devices.

This research examines the dynamics surrounding the use of knee implants following the issuance of safety notices, which are regulatory communications intended to inform stakeholders about identified risks and required actions. The primary focus of this study is to analyze the impact of these safety notices on clinical decision-making and market behavior, particularly regarding changes in the utilization of specific knee implant models. By adopting a quantitative approach, this study seeks to evaluate the actual influence of safety notices on clinical practices, moving beyond the assumption that these notices inherently lead to improved patient safety and device performance.

The objective of this research is to investigate the relationship between safety notices and their effect on the clinical use of knee implants. Rather than idealizing safety notices, the study aims to critically assess their effectiveness in altering clinical practices, reducing surgical revisions, and influencing the selection of medical devices by healthcare professionals. By focusing on empirical data and regulatory analysis, this research will provide insights into the real-world implications of safety notices, offering an understanding of their role within the broader context of orthopedic care.

1.2 Scientific Relevance

The effectiveness of safety notices as regulatory tools has implications for patient safety and clinical practices within the field of orthopedic surgery. This research employs a quantitative analysis to investigate how safety notices impact the usage of knee implants in clinical settings. Specifically, it examines the timing, variability, and persistence of changes in implant utilization following the issuance of these notices.

Unlike previous studies that focus on the theoretical benefits of safety notices, this research takes a critical approach, questioning the extent to which these notices lead to tangible improvements in clinical outcomes. The study leverages statistical methods, including correlation analysis, machine learning models, and interrupted time series (ITS) analysis, to evaluate the impact of safety notices on implant usage patterns. By dissecting the data, the research aims to provide insights into the effectiveness of these notices in influencing clinical behavior and ensuring patient safety.

This research contributes to the field by offering a data-driven examination of the role of safety notices in the regulatory landscape governing medical devices. It seeks to inform improvements in the formulation and

implementation of safety notices, ensuring that these regulatory tools are better aligned with clinical realities and more effectively integrated into healthcare practices.

1.3 Problem Decomposition

This research utilizes the Context, Input, Process, Product (CIPP) evaluation model (Stufflebeam, 2003) to systematically examine the relationship between safety notices and knee implant utilization. This model provides a structured framework for assessing the various quantitative aspects of the issue, ensuring a comprehensive analysis.

- Context: This segment explores the regulatory environment, market dynamics, and the role of manufacturers in the issuance of safety notices. It considers how these factors influence market share and the adoption of specific knee implant models in clinical settings.
- Input: The primary inputs for this analysis are: safety notices (categorized by their type, timing, and scope), and national registries' implants usage data(categorized by volume, time-period, and country). Statistical methods will be employed to evaluate how these characteristics impact knee implant usage and whether they lead to shifts in clinical practices.
- Process: This component focuses on the dissemination of safety notices and their correlation with changes in healthcare professionals' behaviors. It aims to identify and quantify the causal relationships between the issuance of safety notices and subsequent clinical decisions.
- Product: The outcomes of this analysis include observed changes in knee implant usage patterns and the implications for patient safety protocols and regulatory frameworks. These results will be used to assess the overall effectiveness of safety notices in the context of post-market surveillance.

By applying the CIPP model, this research aims to clarify the mechanisms through which safety notices affect systemic changes in clinical practice and regulatory compliance. The analysis will identify the factors that enhance or hinder the effectiveness of safety notices, providing evidence-based recommendations for improving orthopedic care.

1.4 Research Questions

This thesis adopts a structured Quantitative Research Design Framework to explore the impact of safety notices on knee implant utilization and related clinical outcomes. The research is guided by the following key questions:

1. How do safety notices impact changes in knee implant usage over time?
   - This question is addressed through correlation analysis, machine learning models, and ITS analysis. The research examines both aggregate-level data and detailed monthly data from national registries to identify temporal patterns and shifts in knee implant usage following the issuance of safety notices.

2. What impact do different types of safety notices, categorized by IMDRF codes, have on knee implant usage?
   - By categorizing safety notices according to IMDRF codes, this analysis seeks to understand the distinct effects of varying notice types on knee implant usage. The research will explore whether certain categories of safety notices are more effective in influencing clinical practices than others.

3. How do the results of the analysis inform our understanding of safety notice impacts on knee implant utilization in clinical settings? - This question aims to interpret the findings of the study in the context of real-world clinical dynamics, exploring how safety notices influence implant choices and usage patterns. The research will provide insights into the practical implications of these notices in clinical decision-making and patient care, helping to bridge the gap between analytical outcomes and clinical practices.

By addressing these questions, the research aims to provide an understanding of the impact of safety notices on knee implant usage, with the goal of informing both clinical practitioners and policymakers.

1.5 CoSEM Fit

This thesis is aligned with the foundational principles of the Master of Science in Complex Systems Engineering and Management (CoSEM) program at TU Delft, which emphasizes the integration of technical and societal perspectives in addressing complex system challenges.

- Technical: The study employs advanced data analytics, including time series and econometric models, to analyze the direct impacts of safety notices on implant usage patterns and manufacturer market share. It explores how regulatory actions influence healthcare practices and market dynamics, highlighting the role of technological tools in understanding complex responses within the industry.

- Societal: The societal dimension is explored through a critical review of how safety notices impact clinical decision-making, patient outcomes, and regulatory practices. This examination emphasizes the potential and limitations of safety notices in reshaping healthcare systems and improving patient safety.

The approach taken in this thesis reflects the CoSEM program’s objective to address international challenges where technological solutions are shaped by diverse socio-economic conditions. By focusing on medical devices within a global context, this research aligns with the program’s goal of developing a comprehensive understanding of how technological and societal factors collectively influence innovative solutions in complex settings.

Moreover, the thesis contributes to the CoSEM program's commitment to responsible innovation by critically examining the intended and unintended consequences of safety notices. The research aims to provide insights that enhance patient safety, refine regulatory processes, and improve healthcare outcomes, supporting the vision of integrating technology and policy to address global challenges in healthcare.improvements, approximately 20% of recipients reported dissatisfaction due to persistent pain, functional limitations, and unmet expectations regarding implant longevity (Kahlenberg et al., 2019).

Chapter 2

2.1 Article Selection

The article selection process aimed to ensure a review of studies relevant to the impact of safety notices on knee implant utilization. The goal was to build a foundation of existing knowledge, focusing on knee implant technology, regulatory frameworks, and the marketplace mechanisms. This selection process was necessary for situating the study within the broader discourse on medical device regulation and economic dynamics.

2.1.1 Selection process methodology

A multi-stage selection methodology was applied to curate articles that adhered to academic standards. The process began with identifying key databases known for their repositories of medical and engineering literature, including PubMed, Scopus, and Google Scholar. These databases were selected for their coverage of peer-reviewed articles, clinical studies, and regulatory reports, particularly those focused on medical devices like knee implants.

The following criteria were used to select articles:

1. Publication Date: Articles published within the last ten years to ensure relevance and timeliness of data.
2. Relevance: The articles needed to address the safety, effectiveness, and patient outcomes associated with knee implants, with a focus on regulatory frameworks and the impact of safety notices.
3. Peer-Review Status: Only peer-reviewed articles were included to ensure the academic integrity of the findings.

Selection Process

The initial search resulted in a significant volume of literature, which was then filtered through a two-phase screening process. The first phase involved reviewing titles and abstracts against the inclusion criteria, leading to a preliminary selection of articles. The second phase consisted of a full-text review to confirm relevance and methodological rigor, ensuring that the final selection supported the research objectives.

2.1.2 Search Strings

Specific search strings were designed for each database to conduct a thorough literature review on the impact of safety notices on knee implant utilization. These search strings aimed to capture studies that address technical assessments, regulatory analyses, and the broader implications of safety notices.

Database	Search String	Initial Hits	Relevant Articles
PubMed	(("total knee arthroplasty" OR "knee implant" OR "knee prosthesis") AND ("safety notices" OR "medical device recall") AND ("regulatory compliance"))	350	45
Scopus	(("knee replacement safety" OR "knee implant alerts" OR "prosthesis recalls") AND ("regulatory actions" OR "health regulation"))	275	38
Google Scholar	("knee implant safety AND post-market surveillance" OR "total knee arthroplasty effectiveness AND regulatory compliance")	500+	60

Table 1. Search strings used and relevant results

This strategic search process refined a vast body of literature into a focused set of studies that directly inform the research questions, forming the basis for analyzing the impact of safety notices on knee implant utilization.

2.1.3 Scoping

The scoping stage was executed with precision, adopting a selection approach to distill the initial volume of articles into a collection directly relevant to the inquiry into the effects of safety notices on knee implant utilization. This process was governed by defined criteria, focusing on the specific research interests and the academic significance of the articles.

Focus and Relevance of the Article: Central to the scoping criteria was the relevance of each article to the aspects of the research question, ensuring it addressed the intersection of safety notices with knee implant usage, practice implications, or technology influences.

Number of Citations: The number of citations indicated the acknowledgment of the research within the scientific community, serving as a critical filter in the scoping process. This criterion helped prioritize articles recognized for their contributions to the field.

Type of Publication: The review prioritized peer-reviewed journal articles recognized for their contribution to advancing knowledge through rigorous evaluation processes. This approach aimed at anchoring the review in credible contributions to the field.

2.2 Definition of Core Concepts

To anchor the research within a conceptual framework, the following core concepts are defined: Total knee arthroplasty, safety notices, and medical technology stakeholders.

2.2.1 Total Knee Arthroplasty (TKA)

Total Knee Arthroplasty (TKA) refers to a surgical procedure designed to replace the weight-bearing surfaces of the knee joint to relieve pain and disability. The procedure is typically indicated for patients with severe osteoarthritis or other knee diseases that have not responded to more conservative treatments. The success of TKA depends on various factors, including the design and material of the implant, surgical technique, and patient-specific characteristics. The research examines how these factors interact with regulatory frameworks and safety notices, affecting patient outcomes and clinical practices.

2.2.2 Safety Notices

Safety notices are public communications issued by the implant manufacturer, as part of the post-market surveillance system for medical devices. These notices inform stakeholders—such as healthcare providers, patients, and regulatory authorities—about potential risks associated with medical devices, including knee implants. Safety notices are intended to prompt necessary corrective actions, such as device recalls or modifications to clinical use. The study focuses on how these notices are issued, disseminated, and utilized in clinical practice, particularly in the context of knee implant safety.

2.2.3 Medical Technology Stakeholders

The system of medical technology includes various stakeholders, such as manufacturers, healthcare providers, regulatory authorities, and patients. Each stakeholder has a role in the lifecycle of medical devices, from design and development to clinical use and post-market surveillance. This research examines how these stakeholders interact,

particularly in response to safety notices and regulatory actions, and how these interactions influence the adoption and utilization of knee implants.

2.2.4 European Union Medical Device Regulation (EU MDR)

The EU Medical Device Regulation (MDR) 2017/745, which came into effect in May 2021, represents an overhaul of the regulatory framework for medical devices in the European Union. The MDR replaces the previous Medical Device Directive (MDD) and introduces more stringent requirements for clinical evaluation, post-market surveillance, and transparency. Under the MDR, manufacturers are required to maintain ongoing post-market surveillance systems to monitor the performance and safety of their devices throughout their lifecycle. This includes the mandatory issuance of safety notices when devices pose a risk to health and safety. The regulation also introduces a unique device identification (UDI) system to enhance traceability and a greater conformity assessment process to ensure that devices meet safety and performance standards. The research acknowledges how these regulatory changes interact with the knee implant market and the effectiveness of safety notices in clinical practice.

2.3 Literature Review Results

The literature review is organized around three areas: advancements in knee implants and patient outcomes, orthopedic device regulation, and healthcare market dynamics. Each section synthesizes findings from the reviewed literature, highlighting trends and critical insights.

2.3.1 Advancements in Knee Implants and Patient Outcomes

The literature on Total Knee Arthroplasty (TKA) documents advancements in implant design and surgical techniques, focusing on the long-term durability of knee implants and patient outcomes. A registered trend is the increasing use of cementless knee arthroplasties, which studies indicate have reduced revision rates due to their long-term survivability (Carlson et al., 2022). This shift towards cementless implants demonstrates ongoing efforts to improve the longevity and functionality of knee implants, which is relevant for reducing the need for secondary surgeries.

Patient outcomes after TKA are influenced by various factors beyond the choice of implant. Research shows that socio-demographic and psychological variables significantly impact recovery and overall surgical success (Wylde et al., 2007; Judge et al., 2012). These findings suggest that advancements in implant design, while important, must be considered alongside patient-specific factors to optimize outcomes.

In addition, patient perceptions of TKA outcomes reveal ongoing challenges. Although many report improved mobility, some continue to experience issues such as chronic pain, indicating that both objective measures of recovery and subjective patient experiences need to be integrated into the evaluation of TKA success (Woolhead et al., 2005).

The literature examines the impact of design modifications on patient-reported outcomes, with studies indicating that even minor changes in implant geometry or materials can influence recovery trajectories (Toossi et al., 2023). This highlights the asymmetrical impact minor factors have on the industry and its performace.

Short-term outcomes following TKA show consistent success rates across different implant systems, though variations in operation duration and early recovery are noted (Molloy et al., 2019). These studies underscore the need for an approach that considers both surgical techniques and patient factors, in addition to technological advancements, to achieve optimal results in TKA.

Author(s)	Year	Title	Topic	Macro Topic
Hamilton WG et al.	2021	Comparison of Existing and New Total Knee Arthroplasty Implant Systems	Comparison of Implant Systems	Advancements and Outcomes in Knee Prosthesis
Toossi N et al.	2023	Does design change in total knee arthroplasty implants affect patient-reported outcomes?	Impact of Design Changes on Outcomes	Advancements and Outcomes in Knee Prosthesis
Carlson BJ et al.	2022	Clinical outcomes and survivorship of cementless triathlon total knee arthroplasties	Cementless Implants' Outcomes	Advancements and Outcomes in Knee Prosthesis
Molloy IB et al.	2019	Short term patient outcomes after total knee arthroplasty: Does the implant matter?	Short-Term Outcomes Analysis	Advancements and Outcomes in Knee Prosthesis
Wylde, V., Dieppe, P., Hewlett, S., & Learmonth, I. D.	2007	Total knee replacement: is it really an effective procedure for all?	Effectiveness Across Populations	Advancements and Outcomes in Knee Prosthesis
Woolhead, G. M., Donovan, J. L., & Dieppe, P. A.	2005	Outcomes of total knee replacement: a qualitative study	Qualitative Insights into Patient Outcomes	Advancements and Outcomes in Knee Prosthesis
Judge, A., Arden, N. K., Cooper, C., Kassim Javaid, M., Carr, A. J., Field, R. E., & Dieppe, P. A.	2012	Predictors of outcomes of total knee replacement surgery	Predictors of Surgical Outcomes	Advancements and Outcomes in Knee Prosthesis

Table 2. Literature review results regarding advancements in the knee arthroplasty sector

2.3.2 Orthopedic Device Regulation

The regulation of orthopedic devices, including knee implants, is marked by evolving frameworks designed to ensure patient safety and device effectiveness. The EU Medical Device Regulation (MDR) 2017/745 introduced stricter requirements for post-market surveillance, compelling manufacturers to collect and analyze data throughout a device's lifecycle. This regulation also mandates the issuance of safety notices when risks are identified, aiming to improve oversight and reduce patient harm (Melvin & Torre, 2019; Vasiljeva et al., 2020).

However, the implementation of MDR has raised concerns about its impact on innovation. The increased regulatory demands, including extensive data collection and analysis, may slow the introduction of new devices, potentially limiting patient access to advanced treatments. The literature suggests that while MDR aims to enhance safety, it also imposes significant burdens on manufacturers, affecting their ability to innovate (Vasiljeva et al., 2020).

Comparisons between regulatory frameworks, such as those in the United States and the European Union, reveal differences in approval processes and post-market requirements. These disparities can lead to variations in how quickly research converts to the product. Such differences pose challenges for global harmonization of medical device regulations, which is critical for ensuring consistent safety and effectiveness across markets (Kramer et al., 2014; Maak & Wylie, 2016).

The literature also addresses the challenges of ensuring safety in the field of medical devices, particularly as knee implants become more advanced. The incorporation of new materials and design features introduces safety concerns that require thorough evaluation. Regulatory bodies have responded by incorporating principles of human factors engineering and demanding stricter safety protocols to reduce the risk of device-related errors and adverse outcomes. However, these measures increase compliance challenges for manufacturers, who must navigate a growing number of regulations while maintaining the commercial viability of their products (Mattox, 2012; Heneghan et al., 2011).

Despite these regulatory efforts, the effectiveness of safety notices and recalls in preventing harm is still under scrutiny. Studies show that the timing and communication of safety notices are crucial in determining their impact on clinical practices. Delays in issuing these notices or failures in effectively communicating risks can undermine their effectiveness, raising questions about the real-world impact of current regulatory frameworks in managing medical device risks (Heneghan et al., 2011).

Author(s)	Year	Title	Topic	Macro Topic
Melvin T. & Torre M.	2019	New medical device regulations: the regulator's view	Overview of New Regulations	Regulatory Oversight and Safety Notices
Kramer D.B. et al.	2014	Ensuring medical device effectiveness and safety: a cross-national comparison of approaches to regulation	Cross-National Regulatory Approaches	Regulatory Oversight and Safety Notices
Mattox E.	2012	Medical devices and patient safety	Importance of Safety in Medical Devices	Regulatory Oversight and Safety Notices
Heneghan C. et al.	2011	Medical-device recalls in the UK and the device-regulation process: retrospective review of safety notices and alerts	Recall Processes and Safety Notices	Regulatory Oversight and Safety Notices
Vasiljeva, K., van Duren, B. H., & Pandit, H.	2020	Changing device regulations in the European Union: impact on research, innovation and clinical practice	EU Regulations Impact	Regulatory Oversight and Safety Notices
Maak, T. G., & Wylie, J. D.	2016	Medical device regulation: A comparison of the United States and the European Union	US vs EU Regulation	Regulatory Oversight and Safety Notices
Antich-Isern, P., Caro-Barri, J., & Aparicio-Blanco, J.	2021	The combination of medical devices and medicinal products revisited from the new European legal framework	EU Legal Framework Analysis	Regulatory Oversight and Safety Notices
Deep, A., Rana, A. C., & Sharma, P. C.	2019	Regulation and clinical investigation of medical device in the European Union	Clinical Investigation in EU	Regulatory Oversight and Safety Notices
Pean, C. A., Lajam, C., Zuckerman, J., & Bosco, J.	2019	Policy and ethical considerations for widespread utilization of generic orthopedic implants	Ethics and Policy in Implant Utilization	Regulatory Oversight and Safety Notices

Table 3. Literature review results regarding regulations in the knee arthroplasty sector

2.3.3 Healthcare Market Dynamics and Stakeholder Roles

The literature on healthcare market dynamics, specifically within the orthopedic medical device sector, shows how market forces and stakeholder interactions shape the development, adoption, and regulation of knee implants. One notable trend is the adoption of open business models that foster collaboration among stakeholders, such as scientists, engineers, healthcare providers, and patients. These models aim to reduce costs and accelerate the market introduction of knee implants while ensuring that these devices meet the clinical needs of end-users. This collaborative approach helps align the technological innovations in knee implants with the practical requirements of surgical procedures and patient outcomes (Davey et al., 2011; Segarra-Oña et al., 2020).

Stakeholder engagement is essential in the development and successful adoption of knee implants. The literature suggests that involving stakeholders throughout the innovation process results in knee implants that are tailored to clinical needs and more likely to gain acceptance in clinical practice. Effective implementation of safety notices, for example, relies heavily on the active participation and communication among manufacturers, healthcare providers,

and regulatory authorities. In the context of knee implants, this collaborative engagement aims at making sure safety notices lead to changes in clinical practice and enhanced patient safety (Lehoux et al., 2014; Sendyona et al., 2016).

Market dynamics, including competition and consolidation, have an impact on the knee implant industry. The structure of healthcare markets influences factors such as pricing, quality, and the adoption of new knee implant technologies. Consolidation in the orthopedic device market, for example, has led to the dominance of a few large manufacturers, which can influence the pace of innovation and the variety of implants available. Regulatory oversight plays a critical role in maintaining a balance between fostering innovation in knee implant technology and ensuring that these devices are safe, effective, and accessible to patients (Gaynor et al., 2015; Lábaj et al., 2018).

Post-market surveillance is important in the context of knee implants, given the potential for device-related complications that can arise after surgery. Monitoring of knee implants once they are in widespread use is essential for identifying issues that may not have been apparent during the initial approval process. This ongoing surveillance allows for timely interventions, such as the issuance of safety notices, which are critical for mitigating risks and ensuring patient safety over the long term. The efficacy of these systems is crucial for maintaining confidence in knee implant technologies and ensuring that patient safety remains a priority (Badnjević et al., 2022; Nüssler, 2023).

Finally, the impact of market consolidation on the knee implant industry has been profound. Between 1999 and 2015, the market for orthopedic devices, including knee implants, experienced significant consolidation, leading to fewer but larger companies dominating the market. This consolidation can affect the diversity of available knee implants and may influence the direction of innovation, often leading to incremental rather than breakthrough advancements. This trend highlights the need for robust regulatory frameworks that can adapt to the changing market dynamics while continuing to protect patient interests in a landscape where a few macro players have significant influence (Piuzzi et al., 2019).

Author(s)	Year	Title	Topic	Macro Topic
Davey, S. M., Brennan, M., Meenan, B. J., & McAdam, R.	2011	Innovation in the medical device sector: an open business model approach for high-tech small firms	Open Business Models	Healthcare Market Dynamics and Stakeholder Roles
Sendyona, S., Odeyemi, I., & Maman, K.	2016	Perceptions and factors affecting pharmaceutical market access: results from a literature review and survey of stakeholders in different settings	Market Access	Healthcare Market Dynamics and Stakeholder Roles
Segarra-Oña, M., Peiró-Signes, Á., & Verma, R.	2020	Fostering innovation through stakeholders' engagement at the healthcare industry: Tapping the right key	Stakeholder Engagement	Healthcare Market Dynamics and Stakeholder Roles
Lehoux P. et al.	2014	How do business model and health technology design influence each other? Insights from a longitudinal case study of three academic spin-offs	Influence of Business Models and Technology	Healthcare Market Dynamics and Stakeholder Roles
Lábaj M. et al.	2018	Market structure and competition in the healthcare industry	Market Structure and Competition	Healthcare Market Dynamics and Stakeholder Roles
Gaynor M. et al.	2015	The industrial organization of health-care markets	Industrial Organization of Healthcare	Healthcare Market Dynamics and Stakeholder Roles
Badnjević A. et al.	2022	Post-market surveillance of medical devices: A review	Post-Market Surveillance	Healthcare Market Dynamics and Stakeholder Roles

Nüssler, A.	2023	The new European Medical Device Regulation: friend or foe for hospitals and patients?	EU Medical Device Regulation	Healthcare Market Dynamics and Stakeholder Roles
Piuzzi, N. S., Ng, M., Song, S., Bigach, S., Khlopas, A., Salas-Vega, S., & Mont, M. A.	2019	Consolidation and maturation of the orthopaedic medical device market between 1999 and 2015	Market Consolidation	Healthcare Market Dynamics and Stakeholder Roles

Table 4. Literature review results regarding stakeholder dynamics in the knee arthroplasty sector

2.4 Knowledge Gap and Research Question

The literature review reveals gaps in understanding the interactions between regulatory frameworks, market dynamics, and advancements in Total Knee Arthroplasty (TKA). Despite improvements in knee implant technology, the alignment between regulatory measures and technological innovation remains incomplete. This misalignment may hinder the effective implementation of safety notices and other regulatory tools, potentially affecting patient outcomes.

The review also identifies a need for more detailed studies on the integration of safety notices into clinical practice and how market dynamics influence the adoption of knee implants. Although regulatory oversight plays a critical role, there is limited empirical evidence on its actual impact on clinical decision-making and patient safety.

Given these gaps, the research question is formulated as:

"How do safety notices regarding specific knee implants affect their usage in clinical settings?"

This research question aims to address the identified gaps by examining the mechanisms through which safety notices and regulatory actions influence clinical practices and implant selection processes. The study seeks to provide insights that can optimize patient care, improve regulatory practices, and enhance stakeholder engagement in the orthopedic domain.

Chapter 3: Research approach

3.1 Methodology

The study adopts a structured quantitative research design to investigate the relationship between the issuance of safety notices and subsequent changes in knee implant utilization rates. The methodology is built around three statistical methods, which allow for the examination of trends over time and the identification of shifts in implant usage that may correlate with the timing of safety notices: correlation, machine learning, and interrupted time series analysis(ITSA).

3.1.1 Data Sources and Selection

Data for this study were obtained from national arthroplasty registries across nine countries, with the Dutch Arthroplasty Register (LROI) serving as a primary source. These registries provide comprehensive, time-specific records of knee implant usage, including detailed, monthly component-level data. The selection of multiple national registries ensures a broad and representative dataset, allowing for cross-national comparisons and enhancing the generalizability of the findings. The study period was selected based on the availability of comprehensive data, ensuring that both pre- and post-notice periods could be analyzed effectively. The other main datasources was the safety notices dataset, provided by the CORE-MD team (Ren et al., 2023), thanks to Professor Caiani (Politecnico di Milano) and Professor Marang-van de Mheen (Technische Universiteit Delft).

3.1.2 Statistical Methods

The analysis employed statistical techniques to examine implant usage trends before and after the publication of safety notices. The time series analysis was conducted at different levels, including overall implant usage trends and trends stratified by the type of safety notice. Regression models with interaction terms were utilized to observe associations between the issuance of safety notices and changes in implant usage. These methods, combined with correlation analysis and machine learning models, allow for the identification of potential correlations between regulatory actions and shifts in clinical practice, without assuming direct causation.

3.1.3 Limitations and Considerations

The study focuses on observing associations rather than establishing causation. The analysis is limited to identifying temporal relationships between safety notices and changes in implant usage, without inferring direct causal relationships. Potential confounding factors, such as changes in clinical guidelines or market dynamics, are acknowledged, and the study is cautious in its interpretation of the results. The use of regression models with interaction terms is intended to isolate the effect of safety notices as much as possible, but the results are presented as indicative of trends rather than definitive conclusions.

3.2 Research Questions

The research is guided by three sub-questions, each addressing a different aspect of the relationship between safety notices and knee implant utilization.

Sub-Question 1: Impact of Safety Notices on Market Share

This sub-question examines how the issuance of safety notices influences the market share of specific knee implant models on an annual basis. The analysis applies statistical methods to observe changes in market share before and after the publication of safety notices. The study does not assume causation but seeks to identify any significant associations between the timing of safety notices and shifts in implant usage. The analysis is conducted using data

from the Dutch Arthroplasty Register (LROI) and national registries from nine countries, combined with the safety notices dateset.This combination of data allows for tracking of market share changes at a model level across multiple regions.

Sub-Question 2: Impact of Safety Notices by Category

This sub-question extends the analysis by categorizing safety notices according to their International Medical Device Regulators Forum (IMDRF) codes. The study aims to observe whether different categories of safety notices are associated with distinct trends in implant usage. The analysis involves creating dummy variables for each category and interacting these with time variables in the statistical models to detect variations in usage trends by notice type. The CORE-MD model, which uses natural language processing techniques to categorize safety notices, is applied to enable a detailed examination of how different types of notices, categorized by IMDRF codes, impact clinical decisions and implant usage (Ren et al., 2023). The study remains focused on identifying associations rather than inferring causation.

Sub-Question 3: Implications of Safety Notices for Patient Safety

The final sub-question reflects on the potential implications of safety notices for patient safety and clinical practices. The analysis considers how safety notices may correlate with broader changes in healthcare practices, such as market withdrawals, updates to patient safety protocols, or shifts in clinical decision-making. This sub-question draws on quantitative findings from the earlier sections, with a focus on understanding how safety notices may influence patient care indirectly through their impact on implant utilization patterns.

3.3 Research Flow Diagram

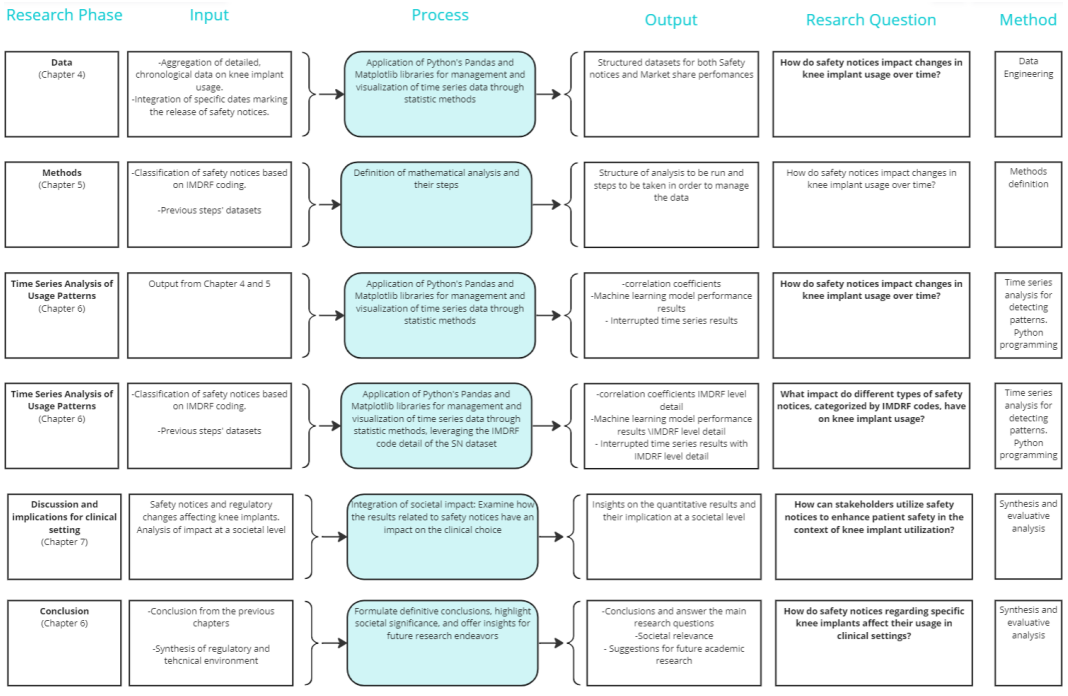


Figure 1. Research Flow Diagram

A research flow diagram is provided to visually represent the research process. This diagram delineates the progression from data collection to data analysis, culminating in the synthesis of findings. Each stage is defined by specific methodologies and analytical tools, illustrating the sequential steps that guide the research. This visual guide

highlights how insights from each phase inform subsequent stages, maintaining a flow throughout the study. The diagram aids in understanding the structured methodology and the interconnectedness of the research phases. Figure 1 displays this diagram.

Chapter 4: The data

4.1 Data Sources: National Implant Registries

This section describes the data sources and methodologies utilized to track the knee implant utilization. The data was obtained from national implant registries, which collect detailed information on knee replacement procedures, including implant models, patient demographics, surgical outcomes, and subsequent revisions. These registries provide longitudinal data, enabling an analysis of implant usage trends over time.

4.1.1 Introduction

National implant registries compile comprehensive data on knee implant procedures, documenting patient demographics, specific implant models, surgical outcomes, and revisions. This data is collected over extended periods, offering insights into implant performance and safety outcomes. The registries used in this study cover nine countries, reflecting a range of healthcare practices and implant market preferences.

4.1.2 Data Collection Methodology

To analyze the impact of safety notices on knee implant utilization, a large and complete dataset was necessary. The following steps outline the data collection process:

4.1.2.1 Data Selection

1. Initial Web and Scholarly Searches: Leveraging Google and Google Scholar, a search was conducted for each of the 199 UN-recognized countries and territories using preliminary queries like "arthroplasty registry [Country Name]" and "national knee implant data [Country Name]." This step aimed to identify any mentions or references to country-specific joint replacement databases.

2. Registry Existence Confirmation: The initial search results were combed through to verify the existence of registries. For countries that yielded potential hits, subsequent steps were taken to ascertain the legitimacy and operational status of the registries.

3. Data Accessibility Evaluation: For each confirmed registry, the availability and accessibility of the data was assesed. Registries that required subscriptions or were behind paywalls, and those lacking online accessibility, were excluded from consideration.

4. Model-Level Detail and Data Continuity Check: Only registries that provided granular model-level details of knee implants and reported annual data for at least four consecutive years of data were advanced for potential inclusion. This ensured that the dataset would support a comprehensive longitudinal analysis.

5. Refinement and Selection: Of the initial 199 countries surveyed, 37 were found to have some form of registry. After applying the inclusion criteria, this number was whittled down to the final 9 registries.

6. Documentation and Finalization: The selected registries were then documented, detailing the years of data coverage, the number of manufacturers, and the specific models tracked. This collection of data forms the backbone of Figure 2, which presents the findings in an organized and scholarly manner.

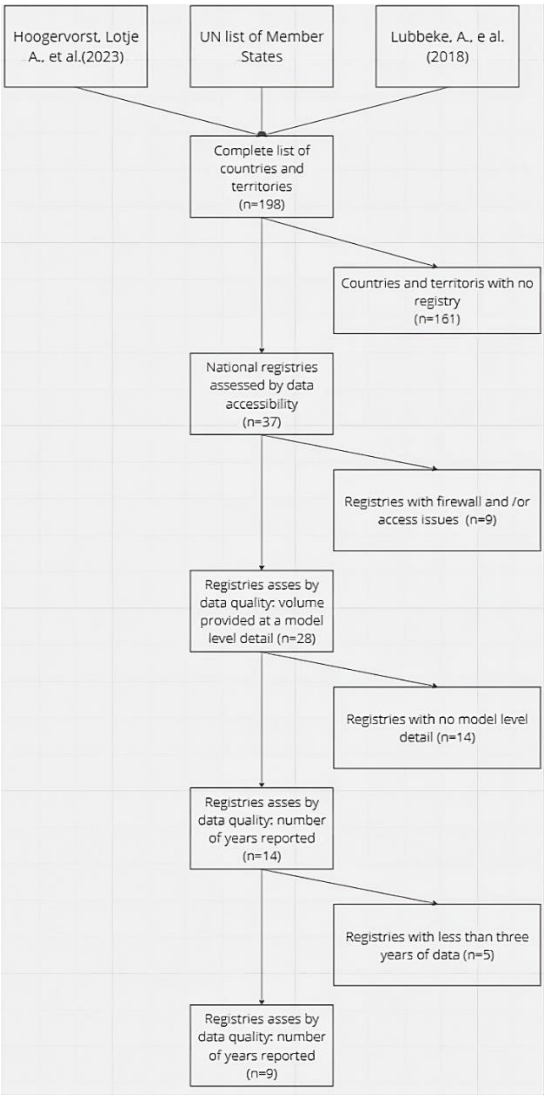


Figure 2. National Arthroplasty registries selection process

4.1.2.2 Extraction, Processing, and Loading

After selecting the national registries, the data underwent a structured process to ensure it was ready for analysis:

1. Data Extraction: Relevant data on knee implant usage was extracted from the annual reports of the selected registries.

2. Data Identification: Key data points, including the total number of implants used annually, categorized by manufacturer and model, were identified

3. Data Exportation: The extracted data was compiled into a preliminary dataset for further processing.

4. Data Processing: The data was standardized to address variations in model names and ensure consistency across different registries. Fuzzy matching techniques were employed to align similar but differently reported names. A custom dictionary was developed to categorize each model.

5. Data Loading: The processed data was loaded into Excel and Python for organization and statistical analysis.

This process ensured that the dataset was consistent and accurately categorized, providing a foundation for observing clinical use trends over time.

4.1.3 Selected Registries

The final dataset aggregated information from national arthroplasty registries across nine countries, covering different periods and reflecting diverse practices in knee replacement surgeries. Table 5 below summarizes the data attributes from each country.

Country	Number of years covered	First Year	Last Year	Number of Manufacturers tracked	Number of Models tracked
Australia	21	2002	2022	9	20
Germany	4	2018	2021	16	34
Finland	24	2000	2023	7	13
Netherlands	8	2015	2022	6	10
New Zealand	18	2005	2022	10	20
Pakistan	6	2014	2019	10	10
Sweden	18	2004	2021	6	17
United States of America	10	2012	2021	4	5
Switzerland	10	2013	2022	6	10
TOTAL	24	2002	2022	26	61

Table 5. List of national registries

The data reflects different market dynamics and preferences in knee implant selection across these healthcare systems. The table below shows the distribution of specific implant models and their market share across the selected registries.

Model	First year registered	Last year registered	Number of National Registries	Average yearly market share
ATTUNE	2012	2022	7	16.26%
GENESIS_II	2000	2023	7	9.01%
PERSONA	2012	2022	7	14.63%
SIGMA	2000	2023	7	16.62%
TRIATHLON	2005	2022	7	18.06%
VANGUARD	2000	2023	7	8.40%
LCS	2002	2022	6	9.01%
NEXGEN	2000	2023	6	30.99%
BALANSYS	2010	2022	4	5.66%
DURACON	2000	2023	4	10.33%

Table 6. List of selected models and their representation across registries

4.1.4 Data Quality and Bias

The dataset's focus on high-income countries limits the representation of global knee arthroplasty practices and echoes broader systemic biases in medical research that favor developed nations. Harris et al. (2017) illustrate the subtle yet pervasive inclination within the academic and healthcare community to undervalue research originating from poorer regions. Such biases influence the accessibility and dissemination of data, shaping the contours of datasets and academic discourse.

The absence of data from a broader spectrum of economies raises questions about equivalence and bias in cross-cultural research. Van de Vijver and Leung (2011) provide a framework for understanding the methodological challenges in ensuring research findings are not skewed by cultural or economic disparities.

The methodology employed in this thesis is rigorous within its defined scope but is constrained by data availability that predominantly represents such affluent countries. Furthermore, the insights provided by Van de Vijver and Leung on bias are relevant here, as they raise important concerns regarding the comparability of results across various socio-economic contexts.

Future research should strive to include more diverse registries, particularly from low- and middle-income countries, to mitigate biases and achieve a more balanced global perspective. Expanding datasets will lead to a more inclusive representation of global health practices, enabling better-informed decisions and policies resonating across diverse socio-economic landscapes.

Figure 3. Visual map of the selected national Arthroplasty registries (light brown)

4.1.5 Dataset End Result

The result of the data collection and processing effort was a structured dataset designed to analyze the market share of knee implant models across different countries and years. The dataset includes columns for country, year, model, and market share, allowing for an examination of how safety notices impacted knee implant usage over time and across countries.

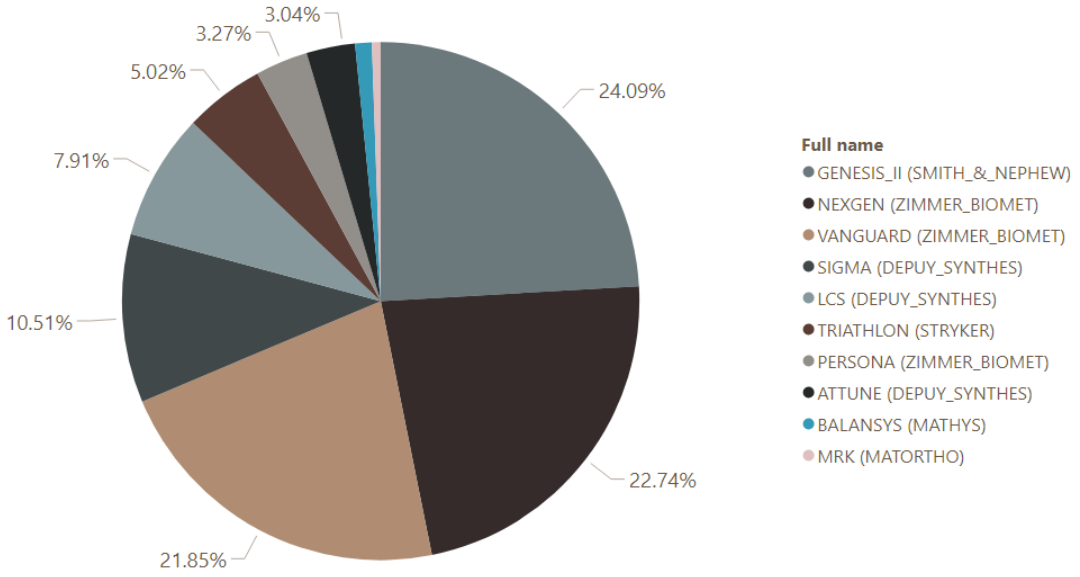


Figure 4. Market Share distribution of TKA implants in the Netherlands (2019)

4.2 Data sources: Safety notices

4.2.1 Introduction

This study leverages data from Hoogervorst et al. (2023), who examined the effectiveness of SNs and registry data in assessing the safety and performance of knee implants across multiple European countries. The CORE-MD PMS Support Tool, developed through a collaboration between 22 European entities, under the European Union's Horizon 2020 CORE-MD project, enhances traditional methods for evaluating high-risk medical devices by translating expert evidence into actionable advice for EU regulators (Fraser et al., 2021).

4.2.2 Data collection methodology

The CORE-MD PMS Support Tool uses natural language processing (NLP) and entity resolution (ER) techniques to improve traditional keyword-based SN retrieval methods. It begins with a collection of SNs from relevant websites using web scraping techniques. NLP algorithms then analyze the textual data to identify SNs based on specific safety-related keywords, linguistic patterns, and semantic structures, ensuring a comprehensive collection of SNs.

An aspect of the CORE-MD tool's methodology is its ER capability, which addresses issues of missing or inconsistent European Medical Device Nomenclature (EMDN) data. By matching SNs to specific devices within an expansive database, the tool accurately categorizes SNs according to severity, the nature of the issue, and relevant EMDN codes. This precise categorization allows for an analysis of SN impacts based on different categories and severities.

The analysis in this thesis utilizes the SN data by employing the date of publication to distinguish the before and after periods, estimating changes in the usage of knee implants associated with the publication of these notices. This approach enables an exploration of how different types of SNs influence clinical practice and patient outcomes, enhancing our understanding of their real-world effects on knee implant usage.

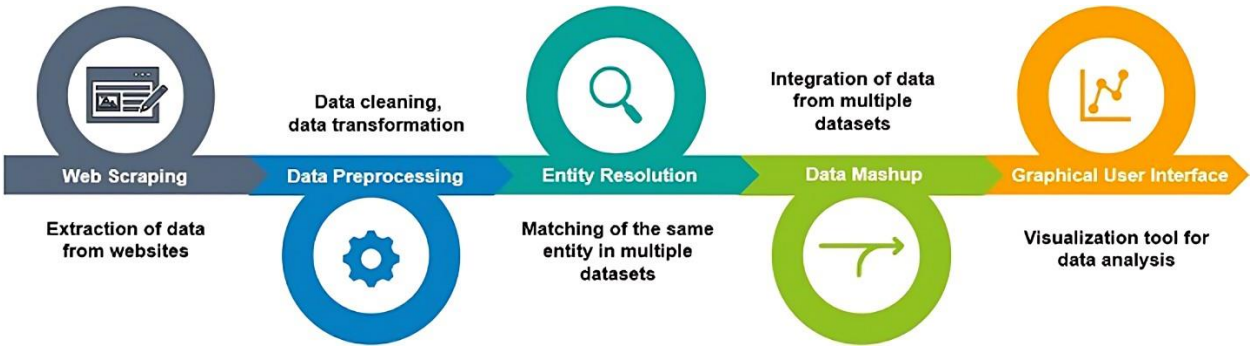


Figure 5. The CORE-MD NLP Pipeline

By integrating different sources through ER, the CORE-MD tool enriches the dataset, ensuring a more accurate and comprehensive aggregation of SN information. Validation of this tool shows a high accuracy rate in assigning manufacturers and EMDN codes to SNs, which is crucial for the reliable analysis of the impact of SNs on knee implant utilization. The CORE-MD model supports the goals of this thesis by providing comprehensive dataset coverage, enhancing precision through SN categorization, and saving time and effort in the data collection process. The model's validation underscores its reliability (Ren et al., 2023)., demonstrating high accuracy (>95%) in manufacturer and EMDN code assignment.

4.2.3 Safety notices: the IMDRF categories

One of the key dimensions utilized in the safety notices dataset is the IMDRF code, which is relevant for categorizing the nature of issues associated with knee implants. The International Medical Device Regulators Forum (IMDRF) codes play an essential role in standardizing the classification of safety notices related to medical devices. These codes provide a consistent framework for identifying and cataloging the nature of problems associated with medical devices, enabling systematic analysis across different regulatory environments and clinical settings.
The usage of IMDRF codes in this thesis investigation is integral for multiple reasons:

1. Standardization: IMDRF codes ensure that safety notices are categorized under a universally recognized classification system. This standardization is used for aggregating and comparing data across different countries and regulatory regimes.

2. Specificity: Each IMDRF code defines a specific type of problem, ranging from manufacturing defects to issues with device labeling or operational failures. This specificity allows for a issue-type based analysis, rather than treating each safety notice the same.

3. Analytical Clarity: By categorizing safety notices according to IMDRF codes, the study can more precisely identify which types of device-related issues most significantly influence clinical practices and implant utilization. This clarity is needed for drawing conclusions that can inform regulatory actions and clinical guidelines.

4. Facilitation of Targeted Interventions: Understanding which IMDRF codes are most frequently associated with changes in implant usage can help healthcare stakeholders prioritize interventions and focus resources on the most critical areas to enhance patient safety.

Table 7 represents the distribution of safety notices analyzed in this study, categorized by IMDRF codes, along with their definitions to explain the specific issues addressed by each code.

IMDRF Code	Count of Safety Notices	Definition
A02	339	Problem associated with any deviations from the documented specifications of the device that relate to nonconformity during manufacture to the design of an item or to specified manufacturing, packaging or shipping processes (out of box problem).
A23	119	Problem associated with failure to process, service, or operate the device according to the manufacturer's recommendations or recognized best practices.
A21	81	Problem associated with device markings/labelling, instructions for use, training and maintenance documentation or guidelines.
A04	63	Problem associated with any deviations from the documented specifications of the device that relate to the limited durability of all material used to construct the device.
A17	59	Problem associated with compatibility between device, patients or substances (medication, body fluid, etc.).
A05	41	Problems associated with mechanical actions or defects, including moving parts or subassemblies.
A24	35	An adverse event (e.g., patient harm) appears to have occurred, but there does not appear to have been a problem with the device or the way it was used.
A26	28	An adverse event appears to have occurred but there is not yet enough information available to classify the device problem.
A18	10	Problem associated with the presence of any unexpected foreign substance found in the device, on its surface or in the package materials, which may affect performance or intended use of the device, or problems that compromise effective decontamination of the device.
A09	6	Problem associated with any deviation from the documented specifications of the device that relate to the end result, data, or test results provided by the device.
A01	4	Problem related to the interaction between the patient and the device.
A20	2	Problem associated with unsatisfactory installation, configuration, and/or setup of a specific device.
Grand Total	787	

Table 7. IMDRF codes, their definitions, and the number of safety notices registered.

To refine the analysis of the impact of safety notices on knee implant market shares, the safety notices are categorized into groups based on their IMDRF codes. Grouping these codes is beneficial as it reduces variability, smooths out data outliers, and increases the number of data points within each category, thus enhancing the robustness and generalizability of the analysis.

Category	IMDRF Codes Included	Description
Manufacturing and Material Defects	A02, A04, A09, A18	Issues related to the physical and material integrity of devices.
Documentation and Compliance Issues	A21, A23	Problems pertaining to the proper documentation and regulatory compliance of the devices.
Adverse Events and Compatibility Issues	A17, A24, A26	Issues involving adverse medical events or compatibility problems with other devices or patient conditions.
Mechanical and Operational Failures	A05	Failures related to the mechanical function or operational performance of the devices.
Setup and Configuration Problems	A20	Difficulties in the initial setup or configuration of the devices.
Patient Interaction Issues	A01	Problems specifically related to the interaction between the device and the patient, which could affect patient safety or device performance.

Table 8. IMDRF codes by category

This dataset, categorized by IMDRF codes and IMDRF categories, forms the empirical basis for analyzing the relationship between specific types of safety notices and changes in knee implant usage patterns. This analysis helps in identifying which device-related issues have substantial impacts on clinical decisions and patient outcomes, thereby contributing to the enhancement of medical device safety and efficacy.

4.2.4 Safety notices: Dataset end result

The integration of safety notices into the post-market surveillance framework was needed for assessing their impact on knee implant utilization. This study leveraged data from the safety notices dataset, focusing on four columns: 'model', 'date', 'IMDRF code', and 'IMDRF group'. Each of these columns played a role in the analytical framework:

1. Model: The 'model' column established a relational link with the knee implant usage data from the National Registry. This linkage served for tracking the usage trends of specific femoral component models before and after the issuance of safety notices.

2. Date: The 'date' of the safety notice pinpointed the temporal event, enabling analysis of market share variations of specific models in relation to the timing of safety notice issuance. This allowed for an assessment of immediate and longitudinal impacts on model utilization following safety alerts.

3. IMDRF code: The 'IMDRF code' served to analyze the differential impacts of various types of safety notices. By clustering safety notices according to the IMDRF classification, the study discerned patterns and impacts associated with different safety issues, ranging from minor inconsistencies to critical failures that necessitated urgent recall actions.

4. IMDRF category: Grouping safety notices by IMDRF codes enhanced the dataset by organizing related safety issues into coherent categories, such as Manufacturing and Material Defects, Documentation and Compliance Issues, and others. This grouping reduced the impact of outliers and increased the number of data points available for each category, smoothing variability and providing a clearer analysis of trends and impacts across similar types of safety notices.

The end product of this analysis was a table summarizing these key columns, which was used to assess the relationship between safety notices and changes in the market dynamics of knee implants. This table not only reflected the direct impacts of safety notices but also provided insights into regulatory effectiveness and implications for clinical practice.

4.2.5 Safety notices: Distribution by manufacturer and model

The analysis of safety notices (SNs) distributed across manufacturers and models demonstrates a significant aggregation among prominent players within the orthopedic device sector. For instance, Zimmer Biomet's NexGen model comprises 30.88% of total SNs, evidencing substantial regulatory scrutiny. This model, along with others like the Vanguard model from the same manufacturer and Stryker's Triathlon, indicates a clear focus on a subset of products that hold significant market shares, as shown in Figure 6.

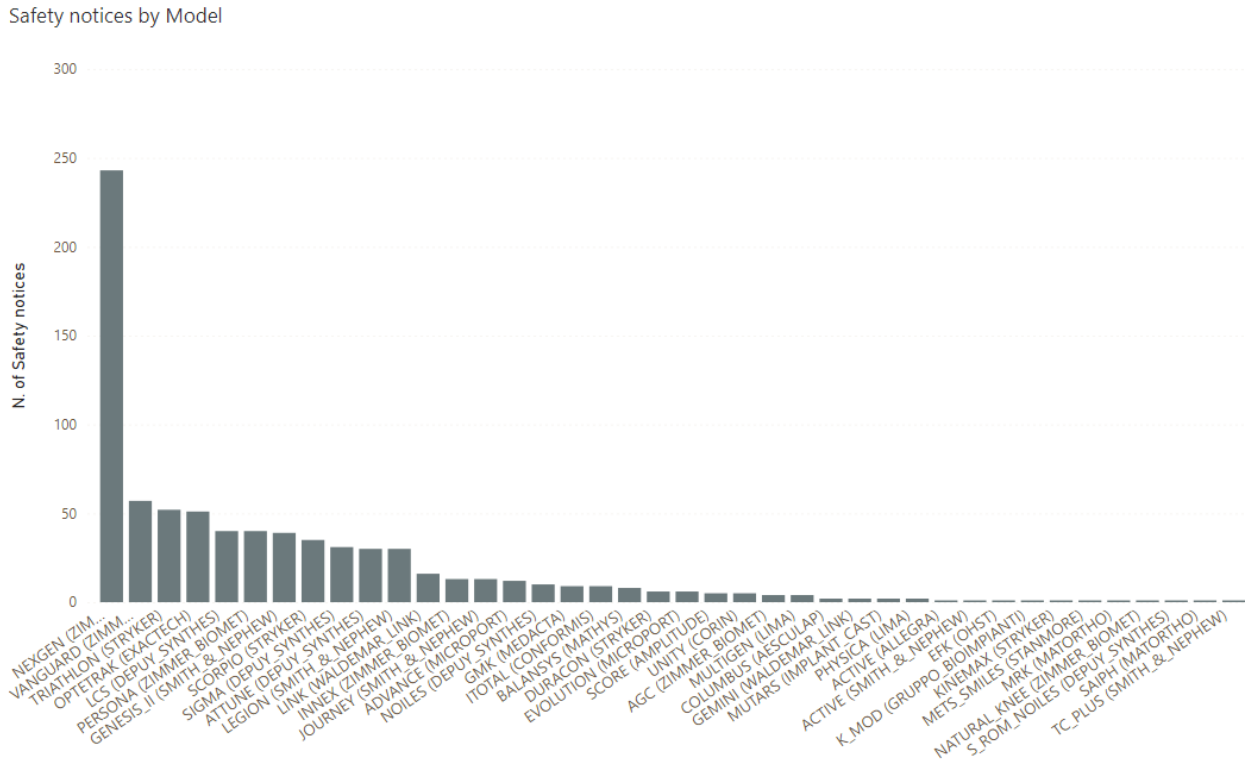


Figure 6. Distribution of Safety notices by Model

The concentration of SNs among these models is corroborated by their registration across countries and longevity in national registries, as detailed in Table 7 and figure 6. Models such as GENESIS II, SIGMA, and TRIATHLON have been present across multiple registries since the early 2000s and continue to be used up to 2023. This usage across diverse national contexts underscores their market penetration and visibility.

This observation aligns with the distribution of SNs; the models with the highest volume of notices are those with the broadest deployment and longest market presence. Therefore, the prevalence of SNs among these models should be interpreted within the context of their market dominance rather than as isolated indicators of product quality or safety deficiencies, as the relative frequency by which SNs occur may be similar. The alignment of market presence with the frequency of regulatory notices illustrates a correlation where the most utilized models are subject to greater regulatory oversight due to their impact on a larger patient population.

4.2.6 Safety notices: Industrial trends

This additional analysis provides an overview of the annual distribution of safety notices (SNs) and the growth in total knee (TK) surgeries per 100,000 inhabitants across OECD-30 and OECD-32 countries, focusing on the years with overlapping data.

From 2000 to 2008, data from OECD-30 countries indicates an increase in the rate of knee surgeries per 100,000 inhabitants, escalating from 60.2 to 108.9. This timeframe shows a consistent rise in surgery rates, with annual growth fluctuating yet remaining positive. The number of safety notices during these years varied, with a notable peak of 48 notices in 2004.

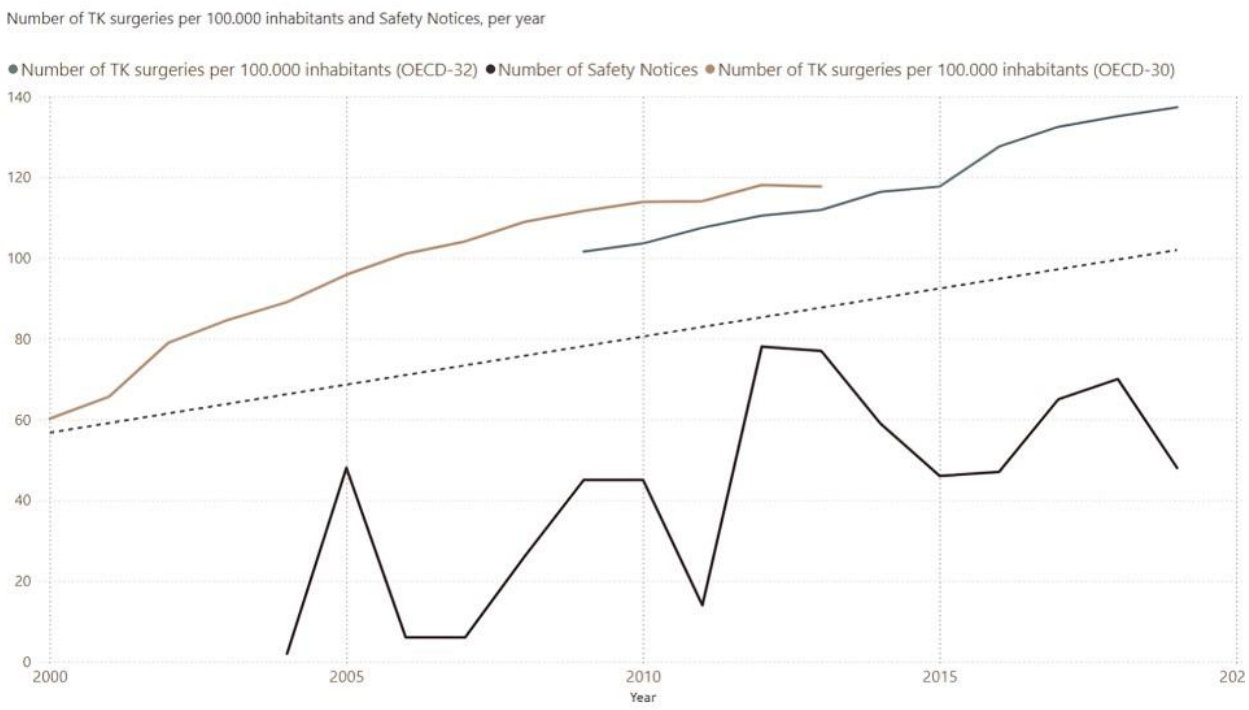


Figure 7. Number of TKA surgeries per 100.000 inhabitants and number of SNs for OECD countries, per year

The dataset expanded in 2009 to include OECD-32 countries. This transition allowed for an additional comparison of knee surgery growth rates across the two datasets. Post-2009, the OECD-32 data continues to display consistent increases in surgery rates, ranging from 1% to 8% annually, with a noticeable rise in 2016.

Regarding safety notices, their annual issuance also shows variation, with a significant volume of notices recorded in 2012 and 2013, totaling 78 and 77, respectively. This data does not infer any specific trends or direct relationships between the frequency of safety notices and the growth in surgery rates, focusing solely on presenting the occurrences and variations noted year over year. It mainly serves to contextualize the market environment in which the study operates, giving the reader a greater understanding of the TKA system.

4.3 Additional dataset: The LROI dataset

In addition to the aggregate-level data from national implant registries that were publicly available, we obtained more detailed procedure-level data from the Dutch LROI (Landelijke Registratie Orthopedische Implantaten) which was used for the Interrupted Time Series (ITS) analysis. The LROI dataset was detailed, containing all records of total knee arthroplasty (TKA) surgeries performed in the Netherlands from 2007 until 2022. Each row in this dataset represented a single TKA surgery, providing atomic granularity.

The LROI dataset offered advantages for ITS analysis:

- Monthly Analysis: The dataset included detail of TKA surgeries, allowing for a more detailed ITS analysis on a monthly basis, as opposed to the yearly granularity of other national registries implant usage.

- Detailed Component Data: The dataset recorded the components used in each surgery, including the femur component and the fixation type (cemented or cementless) which allowed for detailed analysis of the specific implant for which the safety notice was published.

- Comprehensive Coverage: The dataset covered a range of years spanning from 2007 until 2022, providing an appropriate temporal framework for analyzing the impact of safety notices.

For Research Question 1 (RQ1), the analysis utilized the first safety notice per model and fixation type, as derived from the LROI dataset. This approach assessed the impact of safety notices on the market share of knee implants with a higher degree of precision than using aggregate data.
For Research Question 2 (RQ2), the analysis incorporated an additional column for the IMDRF (International Medical Device Regulators Forum) code. This allowed for an examination of the impact of safety notices categorized by IMDRF codes on the market share of knee implants. Each analysis was conducted per model and fixation type, using the first safety notice for each category.

By leveraging the data from the LROI dataset, this study provided a more granular understanding of the effects of safety notices on knee implant usage, enhancing the robustness and specificity of the findings.

Chapter 5: Methods

5.1 Data Integration Approach

To analyze the relationship between safety notices and knee implant usage, it was essential to integrate data from the different sources. The primary task was to link the safety notices (SN) dataset with the national registry dataset. This integration was necessary to observe how safety notices influence the market share of knee implant models over time. Do achieve so, 2 were the main steps taken:

- Standardization of Model Names: Before linking, model names in both datasets were standardized. This involved correcting any discrepancies in naming conventions, such as variations in abbreviations or spelling, to ensure that the same models were consistently identified across datasets
- Linking Strategy: The integration was performed using the 'model' column as the primary key. This approach allowed for the alignment of SN data with the corresponding model usage data from national registries, ensuring that each model's safety notice history could be linked to its market share data.

This integration process was necessary for answering the research questions, particularly the quantitative points.

5.2 The dependent variable: market share

The dependent variable in the study is the market share of knee implant models. Market share was chosen over absolute numbers of surgeries to account for variations in overall surgery rates that could obscure real changes in clinical preferences. By focusing on market share, the study aimed to detect shifts in the preference for specific implant models following the issuance of safety notices.

The formula used to calculate the market share of a specific knee implant model per year and country was:

$$\text{Market Share}_{\text{model, year, country}} = \left(\frac{\text{Number of surgeries using the model in the specific year and country}}{\text{Total knee surgeries in the same year and country}}\right) \times 100$$

This calculation was applied across models, years, and countries. Tracking changes in market share provided insights into how safety notices influenced clinical decision-making. This analysis directly addressed the quantitative research questions concerning the impact of safety notices on the market dynamics of knee implants.

5.3 Methods: correlation analysis

To explore the relationship between the issuance of safety notices and changes in the market share of knee implant models, correlation analysis was employed. The analysis focused on the temporal delays in market response to safety notices, with one-year and two-year delays considered to capture immediate and extended impacts.

Correlation Analysis Formula

$$r = \frac{\sum(x_i - \overline{x})(y_i - \overline{y})}{\sqrt{\sum(x_i - \overline{x})^2 \sum(y_i - \overline{y})^2}}$$

Where:
x_i represents the number of safety notices issued in year t,
y_i represents the market share of the implant model in years t+1 or t+2,
$\overline{x}$ and $\overline{y}$ are the means of the safety notices and market shares respectively.

Data for the analysis was grouped by individual implant models (column 'Model_new'), and entries lacking complete data for both market share changes (column 'Delta_MS_change_Model') and safety notices from the previous year (column 'SN_Model_Global_prev_year') were excluded. Models with zero market share or absent safety notices were also excluded to ensure the robustness of the analysis, which focused on models with relevant market share data and a significant number of SNs.

This approach provided insights into the immediate and extended impacts of safety notices:

- Immediate Impact: The correlation with a one-year delay investigated whether the issuance of safety notices had an immediate impact on market share in the following year.

- Extended Impact: The correlation with a two-year delay assessed whether the effects of safety notices persisted or became more pronounced over a longer timeframe, indicating deeper market adjustments or delayed responses from regulatory and clinical bodies.

Through this methodology, we could better understand the temporal dynamics between regulatory actions and market behavior, illustrating the responsiveness of manufacturers and healthcare providers to safety concerns raised by regulatory bodies.

5.4 Methods: machine learning models

To capture potentially non-linear relationships that could not be evident through traditional statistical methods, machine learning models were employed. These models were useful in analyzing interactions between variables that could influence the market share of knee implant models. Three main model architectures were selected: Random Forest, Neural Network, and XG Boost.

5.4.1 Random Forest

Random Forest, an ensemble learning technique, was selected for its ability to reduce overfitting while maintaining accuracy. The model constructs multiple decision trees and averages their outputs for predictions on the market share change after safety notice publications.

$$\hat{y}(x) = \frac{1}{N}\sum_{k=1}^{N} h(x, \Theta_k)$$

Where $h(x, \Theta_k)$ represents the prediction of the k-th decision tree, Θ_k denotes the randomness in the tree construction, and N is the number of trees. The aggregation of multiple decision trees helped improve generalization error by reducing variance without substantially increasing bias.

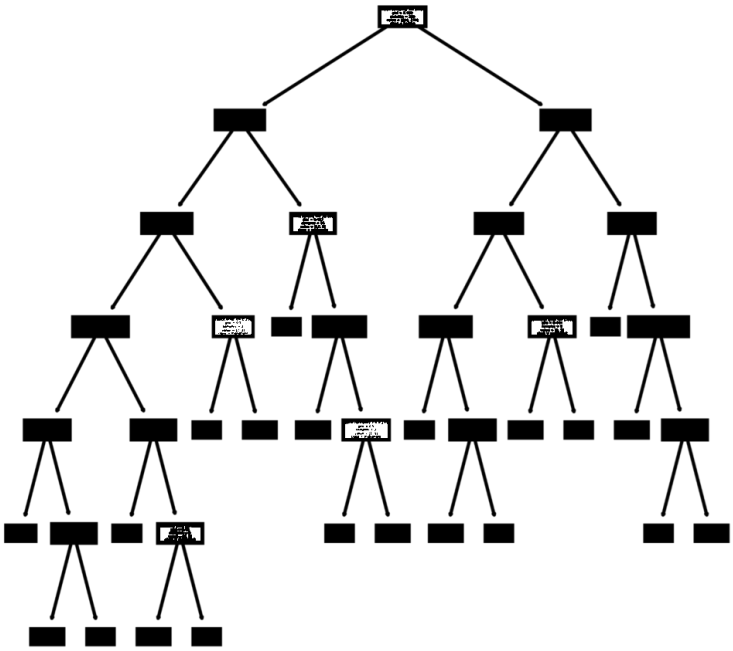


Figure 8. Schematic view of the Random Forest model

5.4.2 Neural Network

Neural Networks were used because of their capability in modeling high-dimensional interactions in a structured way. Neural Networks consist of layers of neurons where each neuron connects to several others and passes signals forward. At each layer, neurons perform weighted sums of inputs from the previous layer, add a bias, and then apply an activation function to introduce non-linearity, enabling the network to learn complex patterns:

$$y = \sigma_2(W_2 \cdot \sigma_1(W_1 \cdot x + b_1) + b_2)$$

Here, W represents the matrix of weights, x is the input vector to the neuron, b is the bias, σ denotes the activation function such as the sigmoid or ReLU.

The network's ability to adjust weights and biases through backpropagation—a method of refining these parameters by minimizing the loss function—allowed it to model highly intricate relationships. For this study, the network architecture included multiple hidden layers, each designed to capture different aspects of the data's structure.

5.4.3 XG Boost

XGBoost, a variant of Gradient Boosting, was used due to its regularization techniques which enhance performance by controlling over-fitting. This was particularly useful given the limitations of our datasets, specifically the annual data from registries. It built upon the principle of boosting by combining multiple weak predictive models to form a strong predictor. The core idea was to successively refine approximations, adding new models that addressed previous errors:

$$\widehat{y_i^{(t)}} = \widehat{y_i^{(t-1)}} + \eta f_t(x_i)$$

And

$$\text{Obj} = \sum_{i=1}^{n} L(\hat{y}_i, y_i) + \sum_{k=1}^{K} \Omega(f_k)$$

Where $\widehat{y_i^{(t)}}$ is the prediction at step t, f_t is the tree added at step t, η represents the learning rate. Each successive tree is fitted on the residual errors of the preceding trees, continuously improving the model's accuracy.

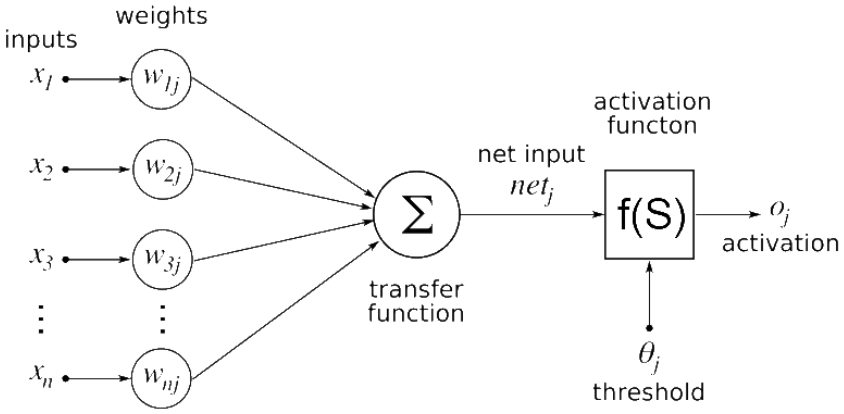


Figure 9. Schematic visual on the mechanisms behind a Neural Network

5.5 Methods: interrupted time series analysis

In assessing the impact of safety notices on the market share of knee implant models, Interrupted Time Series (ITS) analysis was employed, providing a methodological advantage over prior correlation analyses. Previous methods related changes in market share to either the year before or the average of the entire period preceding the intervention, failing to account for possible ongoing trends in the pre-publication period. Unlike these methods, ITS analysis considers the pre-publication trend, enabling the estimation of both the immediate impact on the level and changes in the trend relative to this baseline. This approach isolated the effect of the intervention from other variables by contrasting the observed post-intervention trend in outcomes with a hypothetical scenario in which the intervention did not occur, thus providing a more precise assessment of the impact of safety notices.

For this study, the Dutch LROI dataset on total knee arthroplasty (TKA) surgeries was employed due to its detailed recording of surgery dates, offering finer granularity of data on implant use trends compared to the yearly aggregated data from other national registries. This dataset allowed for more precise tracking of implant usage trends and facilitated a more detailed analysis of the immediate impacts of safety notices.

The primary tool for ITS was segmented regression analysis, which evaluated changes in the level and trend of the market share following the issuance of safety notices. Mathematically, the model can be expressed as:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 T \times X_t + \epsilon_t$$

This formula represents the segmented regression model for ITS analysis, where:

Y_t is the market share of the knee implant model at time t,
T represents time since the start of the study,

X_t is a dummy variable indicating the pre-intervention period (coded 0) or the post-intervention period (coded 1),
β_0 is the intercept or the baseline level of the outcome at the start of the study,
β_1 is the slope of the outcome over time before the intervention, thereby indicating the pre-intervention trend
β_2 represents the change in the level of the outcome immediately following the intervention,
β_3 is the change in the trend of the outcome following the intervention, relative to the pre-intervention trend
ϵ_t is the error term.

This model was adjusted for autocorrelation and other serial dependencies common in time series data to ensure robust estimation of the intervention effects. Techniques like the autoregressive integrated moving average (ARIMA) models were applied to manage correlations between observations over time, enhancing the analytical precision of the study's findings. This approach allowed for a greater understanding of how safety notices influenced the utilization trends of knee implants in clinical settings, leveraging the detailed temporal data from the LROI dataset.

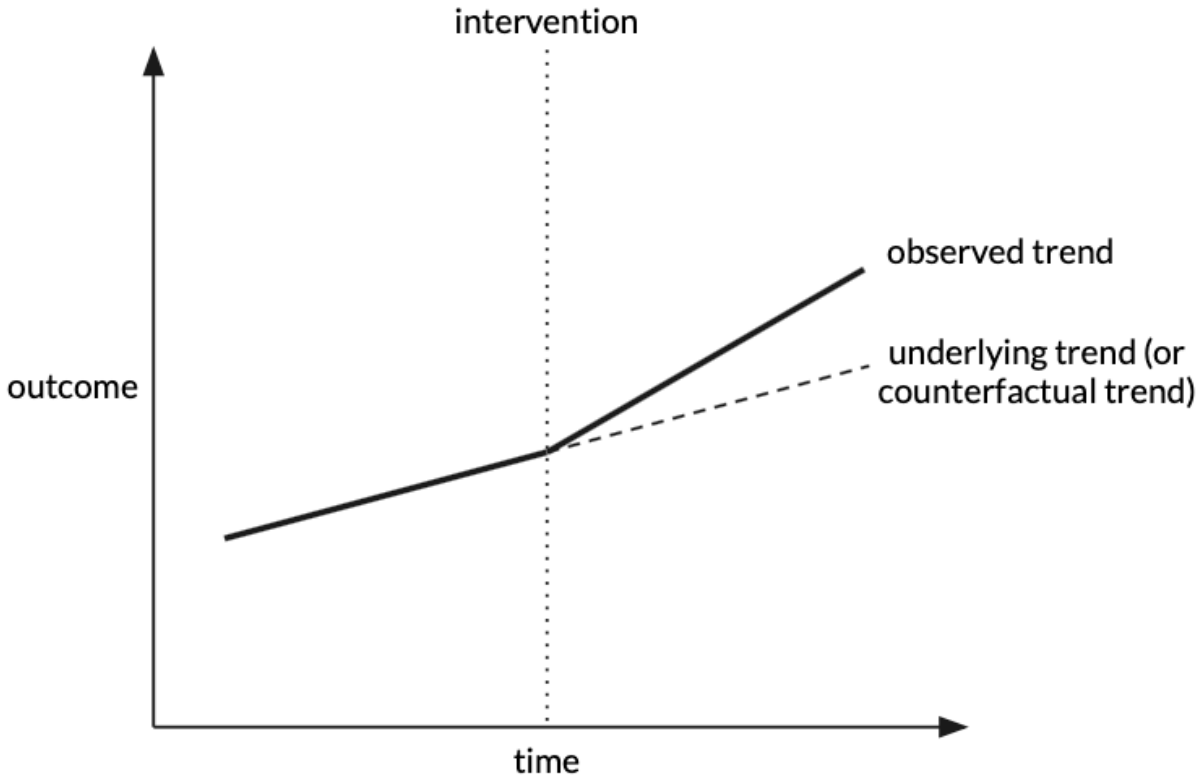


Figure 10. Visual representation of the ITS analysis behaviour modelling

To address autocorrelation and other serial dependencies common in time series analysis, Generalized Linear Model (GLM) with a logistic link function was employed. This model choice, Negative Binomial model, used for count data, is appropriate for handling percentage data, such as market share. The logistic model effectively manages the characteristics of proportion data, where the dependent variable is constrained between zero and one, akin to how the Negative Binomial model is suited for over-dispersed count data.

The Negative Binomial model was specified as follows:

$$\log(\mu_t) = \beta_0 + \beta_1 \cdot T_t + \beta_2 \cdot X_t + \beta_3 \cdot T_t \cdot X_t$$

Where μ_t is the expected count of the outcome variable at time. This model structure allowed to fit the data more appropriately than a simpler Poisson regression, which assumes that the mean and variance of the distribution are equal.
Furthermore, to adjust for seasonal variations and other cyclical effects that might influence the usage trends, we included sinusoidal terms for seasonal adjustment:

$$\log(\mu_t) = \beta_0 + \beta_1 \cdot T_t + \beta_2 \cdot X_t + \beta_3 \cdot T_t \cdot X_t + \beta_4 \cdot \sin\left(\frac{2\pi \cdot \text{month}}{12}\right) + \beta_5 \cdot \cos\left(\frac{2\pi \cdot \text{month}}{12}\right)$$

These additions helped account for consistent seasonal shifts in implant usage, such as variations due to fiscal cycles or holiday periods, ensuring that the analysis robustly isolated the effect of safety notices from other confounding variables. The ITS analysis thus provided a tool to understand the dynamics of how safety notices influenced clinical practices and decision-making at a population level, further enriching the study's contributions to the discourse on medical device safety and regulatory effectiveness.

5.5.1 Selection of suitable models for the ITS analysis

To ensure the integrity and relevance of the Interrupted Time Series (ITS) analysis, a systematic selection of knee implants was necessary. This process was critical for validating the impact of safety notices on implant usage and ensuring statistical robustness.

Identification of Registered Safety Notices: Initially, implants with at least one registered safety notice were selected. This step aligned the study with its objective to examine the effects of regulatory actions on implant usage.

Assessment of Data Availability: Implants not present in the LROI dataset were excluded. This step focused the analysis on models with accessible data, essential for conducting a reliable analysis.

Determination of Surgical Volume: Implants were required to have a minimum of 50 surgeries both before and after the issuance of a safety notice and spread across at least 5 months before and 5 months after the event. This threshold was set to ensure a sufficient sample size for the ITS analysis, thereby minimizing the influence of outliers and random variations that could distort the analysis results.

The following table highlights the selected femur models used in the study, each meeting the criteria outlined for ITS analysis. The 'Before' and 'After' columns represent the counts of surgeries before and after safety notices, ensuring substantial data was available to assess the temporal effects of these notices.

Model	date	Occurrences pre-event	Occurrences after-event	fixation
AGC	21/07/2015	5367	328	
ATTUNE	26/2/2021	3679	4057	Cemented
BALANSYS	29/01/2014	1337	3310	
DURACON	20/09/2007	72	298	
JOURNEY	03/01/2014	1203	1925	
MRK	31/12/2021	1414	516	
SAIPH	25/03/2022	63	57	
TC_PLUS	10/06/2008	167	3952	
VANGUARD	17/10/2016	29963	32833	

Table 9. Selection of implant model used for the ITS and key variables used

Given the detailed LROI data available, the ATTUNE model was divided into cemented and cementless types. This division allowed for a more detailed examination of how different types of implants respond to safety notices, thereby providing nuanced insights into each sub-model's performance and safety profile.
This structured approach helped mitigate the risk of spurious results due to insufficient data or extreme variations in implant usage, enhancing the study's reliability and the validity of its findings.
Figure 9 illustrates these steps and the corresponding counts of implants filtered at each stage, providing a clear and transparent visual representation of the methodology applied. This flowchart supports the study's reproducibility and underscores the systematic approach taken to ensure data quality and adequacy for the ITS analysis.

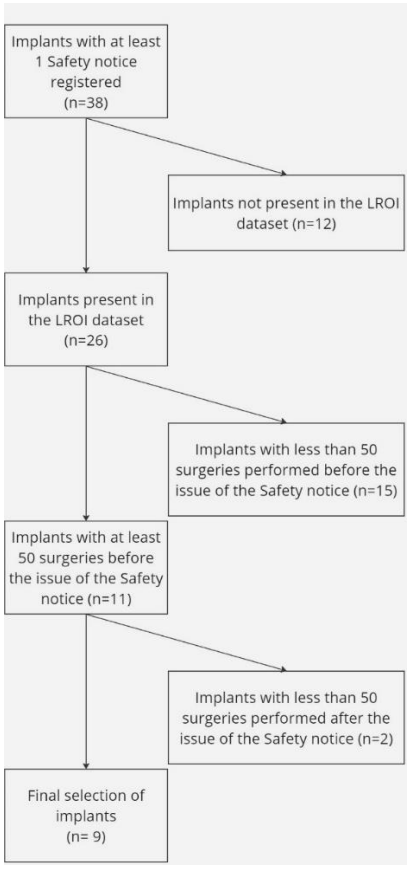


Figure 11. Selection process of LROI implants for ITS analysis

Chapter 6: Results

6.1 Correlation analysis

Correlation analysis assessed the strength and direction of the linear relationship between two variables: the number of SNs issued in year t and the changes in MS in subsequent years t+1 and t+2. Pearson's correlation coefficient, which ranges from -1 to 1, was used to quantify this relationship:

- A positive coefficient indicates that an increase in SNs is associated with an increase in market share.
- A negative coefficient suggests that an increase in SNs corresponds with a decrease in market share.
- A coefficient close to 0 indicates no linear relationship.

The p-value associated with each correlation coefficient indicates the statistical significance of the result. A p-value less than 0.05 was used as threshold for statistical significance.

For each eligible model, Pearson's correlation coefficients and corresponding p-values were calculated to assess the linear relationship between the changes in market share and the number of safety notices issued the previous year. The analysis was performed across different countries, and the correlation coefficients were averaged to provide a comprehensive view of the impact on a global scale.

6.1.1 Results

6.1.1.1 1-year lag

The analysis with a one-year lag generally showed weak and statistically non-significant correlations between the number of SNs and changes in MS across most knee implant models. However, some models did exhibit significant correlations:

Model	Correlation	P-Value
ADVANCE	-0.511673	0.0357716
AGC	0.18078	0.306235
ATTUNE	0.0229856	0.874108
BALANSYS	-0.0437375	0.815277
DURACON	-0.0468917	0.765251
EVOLUTION	0.829214	0.010913
GENESIS_II	0.00735029	0.945183
GMK	0.228973	0.331525
INNEX	0.180189	0.618387
JOURNEY	0.501179	0.0288188
LCS	-0.19666	0.138978
LEGION	-0.127367	0.638309
LINK	-0.0541416	0.776293
MRK	-0.381581	0.526218
NATURAL_KNEE	-0.129481	0.704363
NEXGEN	-0.0238572	0.822392
OPTETRAK	0.597587	0.210322
PERSONA	-0.0541946	0.711501
SCORE	-1	1
SCORPIO	-0.16497	0.556836
SIGMA	-0.0317694	0.758634
TRIATHLON	0.0819879	0.484372
VANGUARD	-0.04523	0.681046

Table 10. Correlation results per model, one-year delay

The analysis of the one-year lag revealed predominantly weak correlations between the number of SNs and changes in market share across various knee implant models. While most correlations were statistically non-significant, a few models demonstrated notable correlations:

- The 'ADVANCE' model showed a negative correlation (-0.511673, p = 0.0357716), indicating that an increase in SNs is associated with a decrease in market share in the following year.
- The 'EVOLUTION' model exhibited a positive correlation (0.829214, p = 0.010913), suggesting that more SNs correspond with an increase in market share.
- The 'JOURNEY' model also had a significant positive correlation (0.501179, p = 0.0288188).

Despite these findings, most models demonstrated high p-values, suggesting minimal impact of SNs on market share within the first year after issuance.

6.1.1.2 2-year lag

Extending the timeline to two years post-SN issuance, the correlations remained weak and were statistically non-significant for all models:

Model	Correlation	P-Value
ADVANCE	-0.40771	0.104272
AGC	0.18078	0.306235
ATTUNE	-0.022455	0.876994
BALANSYS	-0.230224	0.212772
DURACON	0.059899	0.702792
EVOLUTION	-0.024497	0.954087
GENESIS_II	-0.159878	0.132263
GMK	-0.23476	0.319109
INNEX	0.485564	0.154822
JOURNEY	-0.345361	0.147561
LCS	-0.137625	0.302908
LEGION	0.214835	0.424275
LINK	-0.034728	0.855439
NATURAL_KNEE	-0.142022	0.677007
NEXGEN	-0.079375	0.454517
OPTETRAK	-0.009339	0.985992
PERSONA	-0.036269	0.804593
SCORPIO	-0.170694	0.543032
SIGMA	0.088679	0.390237
TRIATHLON	-0.181198	0.119763
VANGUARD	-0.064332	0.558592

Table 11. Correlation results per model, two-year delay

6.1.2 Conclusion

The correlation analyses, both for one-year and two-year lags, revealed a generally weak and statistically non-significant impact of SNs on the market shares of knee implants. The low correlation coefficients and high p-values across most models suggested that the issuance of SNs does not significantly influence market dynamics in the years following publication. This implied that market responses to regulatory actions are likely influenced by additional variables, such as competitive strategies, technological advancements, and changes in clinical practices, which may take longer to manifest.

6.2 Machine Learning models

The primary objective of utilizing machine learning models was to uncover insights into the data that traditional correlation methods might miss. Machine learning techniques, with their ability to handle complex and nonlinear patterns, were expected to provide a broader understanding of the impact of safety notices on market share variations of knee implants.

Input and Output of the Models
Input:

- Global Number of Safety Notices (SNs) Published in Year x for Each Model: This variable accounted for the total number of safety notices issued globally for each knee implant model in a given year.
- Country of Issue: This variable captured the specific country where the market share data is being analyzed, allowing the model to account for regional differences in market behavior.
- Market Share in Year t: This variable represented the market share of each knee implant model in the specific country in the same year as the safety notices.

Output:

- Market Share Change in Year t+1: This was the target variable that the machine learning models aim to predict. It represented the change in market share for each knee implant model in the specific country one year after the issuance of the safety notices.

6.2.1 Results

The three machine learning models used in this analysis were Random Forest Regression, Neural Network, and XGBoost. The performance metrics for these models are summarized in the table below:

Model	MSE	R^2 Score
Random Forest	0.000842	-0.122
Neural Network	0.000899	-0.198
XGBoost	0.001180	-0.573

Table 12. ML models performances

Despite the theoretical robustness of Random Forest, its practical application showed inadequacy in aligning predictions with real-world market behaviors, as indicated by its negative R^2 score. Similarly, the Neural Network, although capable of modeling complex relationships, exhibited limitations in capturing the intricate dynamics influencing knee implant market shares, reflected in its negative R^2 score. XGBoost, known for its proficiency with varied datasets, exhibited the poorest performance among the models, with the highest MSE and the most negative R^2 score, indicating significant predictive challenges.

6.2.2 Conclusion

The underwhelming performance metrics across all models highlight the need for enhanced feature selection, model tuning, and data preprocessing. The integration of additional explanatory variables might yield a more robust framework for understanding the drivers behind market share changes. The transition from traditional correlation analysis to machine learning sought to deepen analytical insights but instead highlighted the necessity for more advanced analytical methodologies. The forthcoming section on interrupted time series analysis further explores the temporal impacts of safety notices on market dynamics, aiming to provide a more detailed understanding of how these regulatory measures influence market trends over time.

6.3 Interrupted time series analysis

The objective of employing Interrupted Time Series (ITS) analysis was to assess whether safety notices significantly influenced the usage patterns of knee implants over time. By examining pre-publication trends in implant usage and analyzing both immediate and long-term effects of safety notices, the analysis aimed to uncover how these regulatory actions impacted clinical practice and implant utilization.

6.3.1 Results

To ensure the validity of the ITS analysis, a Dickey-Fuller test was conducted for each implant model to check for stationarity in the time series data. The results are summarized in Table 13a below:

Dickey-Fuller Test Results

Model	ADF Statistic	p-value
AGC	-1.95044	0.308715
Attune	-0.141547	0.94514
Balansys	-4.70505	8.23337e-05
Duracon	-2.45004	0.128108
Journey	-3.81908	0.00271805
MRK	-2.42358	0.135192
Saiph	-1.84024	0.360674
TC Plus	-2.75635	0.064784
Vanguard	-3.30176	0.0147999

Table 13a. Dickey–Fuller test results over market share time series

The Dickey-Fuller test results, in Table 13a, indicated that some of the implant models, such as Balansys and Journey, exhibit stationarity, while others do not. This variation in stationarity levels across models was crucial for interpreting the ITS results, as it suggested that the time series characteristics differ significantly between models, which may influence how each model responds to safety notices.

The detailed ITS results for the knee implant models are presented in the following table:

Model	**β_0**	**β_1**	**β_2**	**β_3**	**β_4**	**β_5**
AGC	-3.231 (0.0000)	-0.0009 (0.004)	0.107 (0.971)	-0.001 (0.957)	-0.065 (0.851)	-0.004 (0.992)
Attune	-2.017 (0.016)	0.0009 (0.275)	0.278 (0.833)	0.000 (0.962)	0.044 (0.931)	-0.096 (0.844)
Balansys	-3.904 (0.002)	-0.0007 (0.299)	1.103 (0.461)	0.001 (0.391)	-0.018 (0.968)	0.026 (0.954)
Duracon	-2.507 (0.503)	0.0015 (0.952)	-0.426 (0.920)	-0.002 (0.936)	0.117 (0.925)	0.070 (0.956)
Journey	-3.281 (0.004)	-0.0001 (0.938)	0.068 (0.964)	0.000 (0.939)	-0.098 (0.859)	0.029 (0.958)
MRK	-3.351 (0.003)	0.0003 (0.660)	0.068 (0.983)	0.000 (0.978)	-0.008 (0.992)	-0.073 (0.927)
Saiph	-6.517 (0.642)	-0.0001 (0.989)	1.868 (0.933)	-0.001 (0.988)	-0.130 (0.987)	0.483 (0.957)
TC Plus	-4.076 (0.324)	-0.0004 (0.977)	1.742 (0.677)	0.000 (0.990)	-0.040 (0.933)	0.023 (0.960)

Vanguard	0.012 (0.966)	0.0003 (0.048)	-0.147 (0.742)	-0.001 (0.118)	0.016 (0.924)	0.005 (0.977)

Table 13b. ITSA results

Interpretation:

- Intercept (β_0): Represented the baseline market share level of the implant model at the start of the study. For instance, the AGC model had a significant intercept coefficient of -3.231 ($p < 0.001$), indicating a low initial market share level.
- Trend Pre-Intervention (β_1): Reflected the trend in market share before the safety notice was issued. The AGC model showed a significant declining trend ($\beta_1 = -0.0009$, $p = 0.004$), suggesting that market dynamics were already shifting before the regulatory intervention. However, most other models did not exhibit significant pre-intervention trends.
- Immediate Change (β_2): Indicated the immediate impact on market share following the safety notice. None of the models showed significant results for this term, suggesting minimal immediate change in market share after the issuance of safety notices.
- Post-Intervention Trend (β_3): Represented the change in the trend of market share following the safety notice relative to the pre-intervention trend. Across all models, there were no significant changes, indicating that safety notices did not substantially alter ongoing trends.
- Sinusoidal Terms (β_4 and β_5): These coefficients adjusted for seasonal variations. The results showed non-significant outcomes for most models, implying that seasonal effects had a minimal impact on the usage of these knee implants.

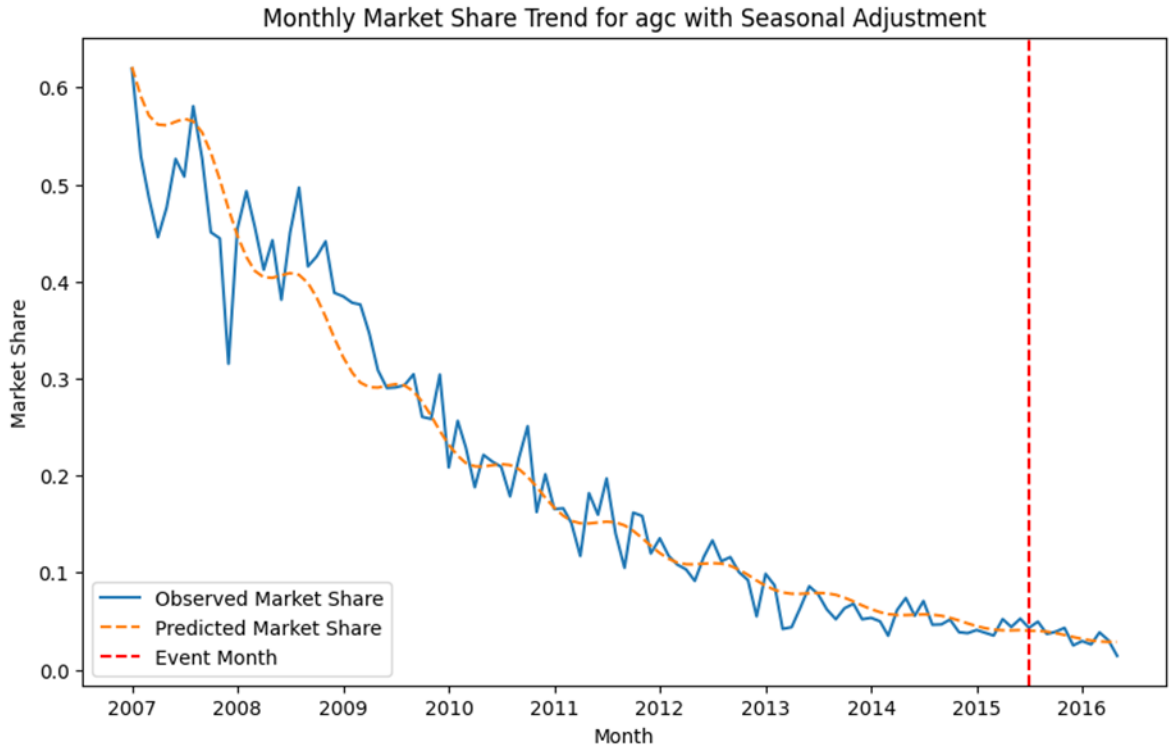
Dickey-Fuller Test Interpretation: The stationarity results from the Dickey-Fuller test were crucial in understanding the validity of the ITS model findings. Non-stationary models like AGC, which had significant pre-intervention trends, suggested that external factors independent of the safety notice may have influenced market share changes. In contrast, for models that demonstrated stationarity (e.g., Balansys, Journey), the ITS results were more robust, indicating that observed trends were likely not driven by underlying time series properties but by other dynamic factors in the market.

6.3.2 Conclusion

The ITS analysis provided insights into how knee implant usage trends respond to safety notices. Key findings include:

- AGC: Exhibited a significant decline in market share before the safety notices ($\beta_1 = -0.0009$, $p = 0.004$), with no subsequent changes after the safety notice, suggesting that other market factors, possibly early signals or informal communications, had already influenced usage patterns before the formal notice.
- Vanguard: Showed a slight increasing trend in market share before the safety notices ($\beta_1 = 0.0003$, $p = 0.048$), with no significant changes post-notice, reinforcing the idea that market behaviors were often established before regulatory actions take effect.

Overall, the results underscored that safety notices may not be the primary driver of changes in clinical practice. Instead, pre-existing trends and market dynamics, often detected by clinicians and market participants ahead of regulatory actions, played a significant role in shaping implant usage.



6.4 Results: analysis per IMDRF code

This section of the chapter investigates the specific impact of safety notices (SNs) categorized by International Medical Device Regulators Forum (IMDRF) codes on the market share of knee implant models. The IMDRF codes provided a standardized system to classify safety notices based on the nature and severity of issues associated with medical devices. The analysis aimed to determine whether different types of safety notices exerted distinct influences on clinical practices and market behavior.

6.4.1 Correlation Analysis by IMDRF Codes

The analysis first examined the correlation between the number of safety notices and market share changes, focusing on different IMDRF codes. This was done for one-year and two-year delays to capture both immediate and delayed market responses.

6.4.1.1 1-year lag

The average correlation coefficients for each IMDRF code indicated the relationship between the number of SNs and changes in market share within one year of their issuance. As shown in Table 14, most correlations were weak and not statistically significant, except for IMDRF code A24, which showed a positive correlation (0.07719, p = 0.0092). This code represents adverse events that have occurred without a clear relation to the implant, suggesting that an increase in SNs under this category is associated with an increase in market share.

IMDRF Code	Average Correlation Coefficient	P-Value
A01	-0.000576	0.9845
A02	0.01816	0.5408
A04	0.04917	0.0976
A05	0.05149	0.0828
A17	-0.02694	0.3644
A18	-0.00300	0.9196
A20	0.01902	0.5219

A21	0.05043	0.0893
A23	-0.01388	0.6402
A24	0.07719	0.0092
A26	-0.03761	0.2053

Table 14. Correlation coefficient between the number of SNs globally by IMDRF code and market share performance, one-year delay

6.4.1.2 2-year lag

Table 15 shows that extending the analysis to two years after the issuance of safety notices revealed no significant correlations for any IMDRF codes. This further supports the notion that safety notices, on average, did not have a substantial impact on knee implant market shares in the longer term.

IMDRF Code	Average Correlation Coefficient	P-Value
A01	-0.0048	0.8725
A02	-0.0218	0.4634
A04	0.0409	0.1687
A05	0.0189	0.5255
A17	-0.0141	0.6357
A18	0.0153	0.6057
A20	0.0131	0.6595
A21	0.0036	0.9039
A23	0.0162	0.5852
A24	-0.0323	0.2773
A26	0.0276	0.3526

Table 15. Correlation coefficient between the number of SNs globally by IMDRF code and market share performance, two-year delay

6.4.1.3 Impact of Safety Notice Categories on Market Share

When analyzing grouped IMDRF codes into broader categories, as shown in Table 16, the correlations remained non-significant for both one-year and two-year delays. The strongest, though still weak, correlations were observed within the categories of Mechanical and Operational Failures and Adverse Events and Compatibility Issues. These categories might be more closely monitored by clinical practitioners, reflecting a slight, albeit not statistically significant, sensitivity to these types of safety notices.

Macro Group	IMDRF Codes	Average Correlation (Year x+1)	P-Value (Year x+1)	Average Correlation (Year x+2)	P-Value (Year x+2)
Manufacturing and Material Defects	A02, A04, A09, A18	0.0322	0.2778	-0.0060	0.8401
Documentation and Compliance Issues	A21, A23	-0.0036	0.9047	0.0163	0.5841
Adverse Events and Compatibility Issues	A17, A24, A26	0.0458	0.1230	-0.0254	0.3931
Mechanical and Operational Failures	A05	0.0515	0.0828	0.0189	0.5255

Setup and Configuration Problems	A20	0.0190	0.5219	0.0131	0.6595
Patient Interaction Issues	A01	-0.0006	0.9845	-0.0048	0.8725

Table 16. Correlation between grouped IMDRF code safety notices and market share changes

Grouping IMDRF codes into broader categories did not reveal significant correlations either. The minor correlations observed in categories such as Mechanical and Operational Failures and Adverse Events and Compatibility Issues suggested that while there may be some sensitivity to these issues, the overall impact of safety notices on market dynamics was limited within the short to medium term.

6.4.2 Machine Learning Models

In light of the inconclusive results from traditional statistical analyses, machine learning models were employed to explore complex interactions and nonlinear relationships within the dataset. These models differed from previous approaches by incorporating the categorization of safety notices (SNs) using IMDRF codes, providing a higher level of data granularity. The goal was to assess whether this detailed input could enhance model performance and yield deeper insights into the specific impact of each IMDRF code on changes in knee implant market share.

6.4.2.1 Results

The performance of the Random Forest and XGBoost models with IMDRF code-level detail is summarized in the table below:

Model	MSE	R^2 Score
Random Forest	0.00089868	0.812039
XG Boost	0.00022559	0.758770

Table 17. Performance of Machine Learning Models with IMDRF Code Level Detail

The XGBoost model's feature importance levels, illustrating the impact of specific IMDRF codes, are shown in the table below:

Feature	Importance
A02 Safety notices for the model	0.07668
A21 Safety notices for the model	0.02504

Table 18. Importance level of the most relevant safety notice types in the model XGBoost

By moving from input data with total SNs to SNs categorized by IMDRF code, the machine learning models offered improved performance and more detailed insights. The Random Forest and XGBoost models both achieved high R^2 scores, indicating their effectiveness in capturing the relationships between SNs and market share changed when detailed IMDRF code data is used.

The importance levels derived from the XGBoost model represent an explainable AI (xAI) approach, which helps identify the variables that have the greatest impact on the model's predictions of market share changes. These importance levels reveal which specific types of safety notices are most influential:

1. A02 Safety notices for the model: These had the highest importance level, suggesting that manufacturing defects and related issues were critical in predicting market share fluctuations.

2. A21 Safety notices for the model: These notices, related to documentation compliance, also significantly impacted market dynamics.

This xAI approach allowed us to understand which factors the model prioritizes, making the decision-making process more transparent and actionable. The significant influence of certain IMDRF codes indicated that detailed regulatory data is crucial for accurately predicting market behaviors.

6.4.3 Interrupted Time Series Analysis

The Interrupted Time Series (ITS) analysis categorized by IMDRF codes revealed variability in how safety notices influence clinical practices across different types of implants. This section focuses on the coefficients for the intercept (β_0), the time trend post-intervention (β_1), and their respective interactions, providing insights into baseline usage levels and trends associated with each IMDRF code. The results were considered alongside the Dickey-Fuller test results to assess the stationarity of the data, which was crucial for interpreting the validity of the ITS model findings.

6.4.3.1 Results

The table below summarizes the ITS model coefficients and their respective p-values for each IMDRF code:

IMDRF Code	β_0	β_1	β_2	β_3	β_4	β_5
A01	-3.26 (<0.01)	0.00 (626.00)	0.15 (0.92)	<0.01 (885.00)	0.01 (0.98)	-0.03 (0.95)
A02	-2.68 (0.25)	0.00 (0.26)	0.29 (0.80)	<0.01 (0.63)	-0.04 (0.91)	0.01 (0.97)
A04	-3.29 (0.41)	0.00 (0.96)	0.66 (0.80)	<0.01 (0.96)	0.04 (929.00)	0.05 (958.00)
A18	4.00 (988.00)	0.00 (0.05)	-0.13 (778.00)	<0.01 (144.00)	12.00 (941.00)	0.00 (998.00)
A21	-2.34 (0.34)	0.00 (0.51)	0.12 (0.88)	<0.01 (0.67)	0.02 (0.91)	0.01 (0.98)
A23	-3.03 (0.00)	-72.51 (0.72)	-0.03 (993.00)	<0.01 (0.94)	0.02 (964.00)	0.01 (974.00)
A24	-3.31 (0.00)	-33.81 (926.00)	-0.11 (949.00)	<0.01 (932.00)	-0.10 (857.00)	0.03 (959.00)
A26	-3.42 (406.00)	0.00 (0.57)	0.73 (0.78)	<0.01 (0.61)	-0.06 (0.93)	0.13 (0.97)

Interpretation:

- **Intercept (β_0):** Represents the baseline market share level of the implant model associated with each IMDRF code. For example, the model with IMDRF code A02 showed an intercept coefficient of -2.68 (p = 0.25), indicating a moderate initial market share level without significant deviations from zero.
- **Trend Pre-Intervention (β_1):** Reflected the trend in market share before the safety notice was issued. For IMDRF code A18, there was a marginally significant trend (β_1 = 0.00, p = 0.05), suggesting that market share changes occurred slightly before the publication of safety notices. This aligned with the category of safety.
- **Immediate Change (β_2):** Indicated the immediate impact on market share following the safety notice. Across all IMDRF codes, none of the models showed significant results for this term, implying minimal immediate changes in market share after the issuance of safety notices.
- **Post-Intervention Trend (β_3):** Represented the change in the trend of market share following the safety notice relative to the pre-intervention trend. The analysis found no significant interaction effects (β_3), indicating that the safety notices did not substantially alter ongoing trends.
- **Sinusoidal Terms (β_4 and β_5):** These coefficients adjusted for seasonal variations. The results showed non-significant outcomes for most models, implying that seasonal effects had minimal impact on the usage of implants associated with these IMDRF codes.

Stationarity and ITS Model Validity: The stationarity results obtained from the Dickey-Fuller test were crucial in understanding the validity of the ITS model findings. Non-stationary models, such as those associated with IMDRF code A18, suggested that market dynamics mighy have been influenced by factors independent of the safety notice. In contrast, other IMDRF codes showed no significant stationarity, leading to less robust ITS results.

Conclusion: These findings showed the limited impact of safety notices on clinical practices, particularly when analyzed through the lens of IMDRF code categorization. The pre-existing trends and stationarity results suggested that market dynamics were influenced by factors preceding the official publication of safety notices. This highlighted the reactive nature of regulatory actions, which often lag shifts in clinical practices.

6.4 Conclusion of data analysis

The analysis in this chapter provided a detailed examination of the relationship between safety notices (SNs) and market share (MS) changes in knee implant models. The correlation analyses, including one-year and two-year lags, consistently showed weak and statistically non-significant impacts of SNs on market share variations. These findings suggested that SNs alone did not significantly influence market dynamics within the observed periods.

The machine learning models were employed to explore more complex interactions within the data. These models, which included detailed inputs such as the number of SNs per IMDRF code and regional market share data, did not fully capture the variations in market share changes. The results indicated that the complexity of market dynamics likely involves factors beyond those considered in the models.

The Interrupted Time Series (ITS) analysis offered a more precise examination of the impact of SNs, particularly when categorized by IMDRF codes. The results showed that not all SNs had the same effect; for example, SNs under IMDRF code A18 showed significant influence, while others, such as A04, had minimal impact. These results highlighted the importance of considering the specific nature of safety notices when evaluating their impact on market behavior.

Overall, the findings suggested that the direct impact of SNs on market share changes was limited. The response of the orthopedic device market to SNs appeaed to be influenced by a broader set of factors, including competitive strategies, technological changes, and clinical practices, which were not fully captured by the methods used in this analysis.

7.Discussion

7.1 Overview of findings

This section synthesizes the findings from Chapter 6, which examined the impact of safety notices on the market shares of knee implant models using correlation analysis, machine learning models, and interrupted time series (ITS) analysis. These methods collectively offered a comprehensive perspective on how regulatory actions influence market behavior.

Correlation analysis showed that safety notices generally have a minimal direct impact on market shares over a two-year period. Most correlations were weak and statistically non-significant. However, significant correlations were observed in the Advance, Evolution, and Journey models. These outliers suggested that, under specific conditions or due to factors, safety notices could have a more pronounced effect on market dynamics.

Machine learning models provided further insights, particularly when incorporating data categorized by International Medical Device Regulators Forum (IMDRF) codes. These models outperformed those without IMDRF categorization, highlighting the importance of detailed regulatory data in predicting market responses. This indicated that the granularity of input data, particularly regarding regulatory classifications, was crucial for understanding market behavior.

ITS analysis produced mixed results, with significant pre-publication trends observed in models like AGC and Vanguard. These trends implied that safety notices could often formalize safety concerns that were already influencing market dynamics prior to their official release. Across all models, the analysis consistently found no significant impact from safety notices after their publication, suggesting that these notices could align with existing trends rather than initiate new ones.

The following discussion will explore these findings in greater depth, examining their implications for our understanding of market dynamics in the orthopedic device sector. The goal is to provide a clearer understanding of how safety notices influence clinical practices and to offer insights that could inform future regulatory strategies.

7.2 Direct impact of safety notices

Safety notices function as regulatory tools to communicate risks associated with medical devices, including knee implants. These notices inform the healthcare community of potential concerns and may influence market dynamics, including changes in the usage of implants. Analyzing the direct impact of these notices involves considering factors such as the frequency and severity of the notices, media coverage, and regulatory responses.

The analysis showed a generally weak and statistically non-significant relationship between the issuance of safety notices and changes in market share across most knee implant models. However, the 'ADVANCE' and 'EVOLUTION' models showed significant correlations, indicating that these cases require further examination to understand the factors influencing market behavior.

Case Analysis of Outliers:

Model	Event Description	Impact Analysis
ADVANCE	In 2016, safety notices (IMDRF A05) were issued for mechanical failures in Italy and the USA.	The clustering of safety notices likely increased market sensitivity, leading to a decrease in market share. This decline was possibly influenced by extensive media coverage.
JOURNEY	In 2018, safety notices (IMDRF A24) addressing adverse events	These notices likely influenced clinical decision-making, reducing the implant's market share.

	and compatibility issues were issued in multiple countries.	
EVOLUTION	From 2015 to 2022, issues were flagged in safety notices (IMDRF A02) concerning manufacturing and material defects.	Despite these concerns, the market share for the EVOLUTION model increased. This suggests that the defects did not significantly affect clinical use, possibly due to risk management strategies by the manufacturer or a strong market position.

Table 20. outlier cases

The literature discusses the role of regulatory frameworks in managing the impact of safety notices. Research by Heneghan et al. (2011) highlights the prevalence of medical device recalls and their implications for patient safety and healthcare costs. Melvin and Torre (2019) describe the requirements under the European Medical Device Regulation (MDR) and the In Vitro Diagnostic Regulation (IVDR), which enforce post-market surveillance to ensure that devices failing to meet safety standards are withdrawn from the market.

In conclusion, the impact of safety notices on market dynamics depends on the specific context of each notice. The 'ADVANCE' model shows that regulatory and public scrutiny can lead to a decrease in market share. In contrast, the 'EVOLUTION' model indicates that strong market presence and manufacturer response can mitigate the effects of safety notices. These findings reflect the interactions between regulatory actions, manufacturer strategies, and market forces within the medical device industry. Regulatory frameworks like the MDR and IVDR play a role in managing these interactions and ensuring the safety of medical devices in the market. Altogether, the results were inconclusive by definition, but showed that, large volumes of SNs did have a directional impact of a model's market presence, although not strictly positive or negative.

7.3 Trust in medical devices

Trust in medical devices, particularly knee implants, is a critical factor in clinical decision-making and market dynamics. The Interrupted Time Series (ITS) analysis of knee implant models offered insight into how safety notices affect market shares and usage patterns. Despite the issuance of safety notices, their impact on the utilization of these devices was often minimal, reflecting the trust that surgeons and other decisionmakers place in familiar implants and the inherent inertia in clinical practice.

The ITS analysis revealed mixed outcomes across different knee implant models. For instance, the AGC model showed a significant negative trend in market share before the safety notice was issued (β_1 = -0.0274, p = 0.004), indicating a decline in usage already underway before the intervention. This pre-intervention trend suggests that market dynamics had already been influenced by factors other than the safety notice, reducing the notice's relevance in altering the trajectory. Similarly, the Vanguard model displayed a positive pre-intervention trend (β_1 = 0.0090, p = 0.048), with an increasing market share before the safety notice, and no significant change post-intervention. These examples indicate that pre-existing trends in implant usage can be strong, thereby diminishing the potential impact of safety notices as observed through ITS analysis. The lack of significant immediate impacts, changes in the post-intervention trend, and the absence of seasonal effects across all models suggest that safety notices alone do not trigger substantial changes in implant usage.

Supporting studies reinforce the ITS findings, showing that trust and familiarity with implants often outweigh the influence of safety notices. Okike et al. (2014) observed that orthopedic surgeons frequently prioritize clinical outcomes and familiarity with implants over economic considerations, often lacking detailed knowledge of implant costs. Wasterlain et al. (2017) confirmed that familiarity is the dominant factor in implant selection, more so than cost. Sharkey et al. (1999) highlighted that patients trust their surgeons to choose implants based on quality, with 97.1% of patients willing to pay more for higher-quality implants. This trust in the surgeon's expertise supports the preference for familiar and trusted devices, regardless of safety notices.

Additional research, again, aligns with these findings. Burns et al. (2018) found that surgeons' preferences are driven by technology and implant characteristics rather than by vendor reputation or cost. Gardezi et al. (2021) noted that while there is growing awareness of costs, the preference for higher-cost items is often due to the perceived greater clinical value, emphasizing the importance of quality and effectiveness over cost.

The analysis suggested that trust in medical devices is heavily influenced by familiarity, perceived quality, and clinical outcomes, which can overshadow the impact of safety notices. Strong pre-intervention trends in implant usage further dilute the effect of these notices, as existing market dynamics are already in motion. These findings underscore the importance of transparency and the provision of comprehensive information on both costs and clinical outcomes to balance economic considerations with quality, thereby sustaining trust in medical devices.

7.4 Information overload

Information overload is increasingly relevant in the context of medical device safety, especially concerning the issuance of safety notices for knee implants. The analysis conducted in this study, particularly the Interrupted Time Series (ITS) analysis, revealed that individual safety notices generally do not lead to significant changes in implant usage. However, when safety notices are issued in rapid succession, as observed with the ADVANCE model in 2016 and the JOURNEY model in 2018, there was a notable reaction in the market. This suggests that the cumulative effect of multiple safety notices, rather than the content of each individual notice, can influence clinical practices.

This phenomenon of information overload is consistent with the broader patterns observed in the medical field. The ITS analysis highlighted that market responses were muted when safety notices were sporadic, but more pronounced when multiple notices were concentrated within a short period. This pattern indicates that the volume of information, when excessive, can overwhelm healthcare providers, leading to little shifts in clinical behavior. This aligns with the findings from the previous discussion on trust in medical devices, where it was noted that strong pre-existing trends in implant usage often diminish the impact of individual safety notices. Although this was found to be the case, correlation results showed that, when multiple notices accumulate rapidly, they may collectively overcome the inertia associated with established clinical practices, prompting more immediate changes in implant usage.

The literature supports this understanding. Studies by Lübbeke et al. (2018) and Gardezi et al. (2021) have shown that excessive information can complicate decision-making processes, leading to decision fatigue among healthcare professionals. This fatigue can result in delayed or reactive changes in clinical practices, rather than proactive and informed decisions. Similarly, Schneller and Wilson (2009) emphasize that the rapid influx of new information can challenge the cognitive capacities of surgeons, disrupting their decision-making and affecting their relationships with suppliers and other stakeholders.

In conclusion, while individual safety notices often have a limited impact, the rapid succession of multiple notices can lead to statistically significant changes in clinical practices, overcoming such information overload. This finding underscores the importance of managing the flow and presentation of safety information to ensure that it is actionable and does not overwhelm healthcare providers. By carefully coordinating the timing and communication of safety notices, regulatory bodies could help mitigate the effects of information overload, thereby enhancing the effectiveness of these notices in influencing clinical decision-making.

7.5 Time and timing

The comparison between Correlation Analysis and Interrupted Time Series (ITS) Analysis reveals that the effects of safety notices (SNs) on the market share of knee implants are complex and time-dependent. Correlation analysis identified statistically significant relationships for specific implant models, such as ADVANCE, EVOLUTION, and JOURNEY, where SNs were associated with changes in market share. These correlations point towards some influence market dynamics, but the impact appears gradual and is likely intertwined with broader market adjustments rather than immediate responses to SNs.

In contrast, ITS analysis, which is designed to detect immediate and long-term changes following an intervention, did not find statistically significant impacts on market share across the models analyzed. The lack of significant results in the ITS model, despite significant correlations in the correlation analysis, suggests that any influence SNs may have on market dynamics is not directly tied to the moment of their issuance. This outcome is supported by the Dickey-Fuller test results, which showed that only the JOURNEY and VANGUARD models exhibited statistically significant stationarity trends in they market share curves. This stationarity indicates that these models' market behaviors were already established and were likely driven by factors preceding the publication of SNs.

Model	Correlation Coefficient	ITS Analysis
ADVANCE	-0.511673 (p = 0.0358)	No statistically significant parameter
EVOLUTION	0.829214 (p = 0.0109)	No statistically significant parameter
JOURNEY	0.501179 (p = 0.0288)	No statistically significant parameter
VANGUARD	-0.04523 (p = 0.6810)	No statistically significant parameter

Table 21. ITS and correlation results

The divergence between these methods underscores the possibility that market responses to safety notices are more reflective of pre-existing trends rather than direct effects of the notices themselves. The observed correlations might be capturing ongoing adjustments in the market that were already underway due to early clinical feedback or informal communications within the healthcare industry, as noted by Davey et al. (2011) and Segarra-Oña et al. (2020) regarding the role of stakeholder engagement in shaping market responses. The ITS results, by failing to show immediate effects, further reinforce the view that SNs confirm rather than cause shifts in market behavior, aligning with the reactive nature of regulatory interventions (Lehoux et al., 2014; Badnjević et al., 2022).

Future work could explore the identification of earlier indicators of market shifts and the interaction of these factors with regulatory actions, potentially leading to more timely and effective interventions.

7.6 Complexity

Incorporating IMDRF codes into machine learning models improves their ability to analyze the impact of safety notices on knee implant market shares. Unlike traditional correlation methods, which failed to show a strong relationship, machine learning models enhanced with IMDRF codes revealed more complex patterns in the data.

Model	Condition	MSE	R^2 Score
Random Forest	Without IMDRF Codes	0.000842	-0.122
Random Forest	With IMDRF Codes	0.00089868	0.812039
XGBoost	Without IMDRF Codes	0.001180	-0.573
XGBoost	With IMDRF Codes	0.00022559	0.758770

Table 22. ML performance comparison: with or without the categorization per IMDRF code

These data points reveal that machine learning models, when enhanced by IMDRF code granularity, can significantly improve in predicting market share changes due to safety notices, indicating a substantial gain in the models' ability to capture complex market dynamics.

The relevance of non-linear dynamics in healthcare is supported by the literature. Davey et al. (2011) discuss how open business models in the medical device sector facilitate innovation by integrating inputs from a broad base of stakeholders, significantly affecting market dynamics in response to regulatory changes. Similarly, Segarra-Oña et al. (2020) highlight the critical role of stakeholder engagement in enhancing the responsiveness of healthcare innovations to market and regulatory demands.

Further literature such as Gaynor et al. (2015), which examines the industrial organization of healthcare markets, and Lábaj et al. (2018), which discusses market structure and competition in healthcare, provide broader context for understanding how non-linear interactions influence market dynamics. These studies suggest that the market's response to regulatory actions is influenced by a confluence of competitive behavior, regulatory compliance, and innovation dynamics, all captured more effectively with the granular data analysis enabled by IMDRF code categorization in machine learning models.

This approach underscores the necessity for advanced analytical tools to navigate the complexities of modern healthcare markets, ensuring that regulatory strategies effectively align with clinical and patient safety needs. By enhancing the granularity of input data, machine learning models not only improve their predictive accuracy but also provide deeper insights into the specific impacts of various types of regulatory actions, thereby offering a more comprehensive view of how diverse regulatory notifications impact medical device markets.

7.7 Regulation and science

The disparity between the rapid advancements in medical science and the slower pace of policy and regulation significantly impacts the relationship between safety notices and market behavior. Scientific research and market innovation in knee implants, as highlighted by studies such as Carlson et al. (2022) on cementless implants and Toossi et al. (2023) on implant design, drive continuous improvements in patient outcomes. These advancements occur in an environment where new technologies are quickly adopted and integrated into clinical practice, often in response to emerging evidence and competitive pressures. In contrast, regulatory frameworks, as discussed by Melvin and Torre (2019) and Vasiljeva et al. (2020), are designed to ensure safety and efficacy, which necessitates a more cautious and deliberate approach. This inherent lag in policy implementation means that by the time safety notices are issued, the scientific community and market may have already moved beyond the concerns addressed by these notices.

This helps in explaining the weak connection between safety notices and clinical usage observed in the study. Safety notices often react to issues that have already been identified and addressed by ongoing research or clinical experience, as suggested by the pre-intervention trends in the ITS analysis. For instance, the decline in usage of the AGC model prior to the safety notice reflects a market already responding to emerging data, independent of regulatory action. The rapid pace of scientific innovation and market adaptation, driven by studies such as those by Molloy et al. (2019) and Gaynor et al. (2015), frequently outstrips the ability of regulatory bodies to issue timely interventions. Consequently, safety notices may have limited impact on clinical practice because the medical community has already adjusted to the new information before official notices are published.

This dynamic reflects the need for regulatory bodies to improve their reaction time and responsiveness to emerging scientific data and market trends, perhaps through more proactive post-market surveillance as advocated by Heneghan et al. (2011) and Badnjević et al. (2022). Bridging the gap between the fast-paced innovation in medical devices and the slower, more cautious approach of regulation is essential for ensuring that safety notices can effectively guide clinical practice and protect patient safety.

7.8 Conclusion and future research

This thesis has examined the research question: "How do safety notices regarding specific knee implants affect their usage in clinical settings?" The analysis conducted throughout the study reveals that the impact of safety notices on clinical practice and market behavior is limited and complex. Safety notices, while designed to inform and guide healthcare providers regarding potential risks associated with medical devices, appear to have a delayed and often non significant influence on clinical decision-making. This outcome reflects the broader context in which scientific advancements and market forces frequently move at a faster pace than regulatory actions, with safety notices tending to react to rather than preempt market trends and clinical practices.

The study's findings indicate that safety notices, despite their regulatory intent, do not significantly alter knee implant usage patterns. The dynamics of clinical and market behavior appear to be influenced more by factors such as technological advancements, surgeon preferences, and established trends in clinical outcomes than by the issuance of safety notices. This suggests a disconnect between the issuance of safety notices and their intended impact on clinical practice.

This study has limitations that must be acknowledged for future research. The use of secondary data, including databases and published safety notices, may not capture all factors influencing clinical decisions, such as the intricacies of surgeon-patient interactions, institutional policies, and informal knowledge exchange. Additionally, the analytical methods used, such as correlation analysis and machine learning models, may not fully address the complex nature of how safety notices interact with market dynamics and clinical practices.

Future research should incorporate more comprehensive data collection methods, including primary data through interviews, focus groups, and surveys with healthcare providers, to gain deeper insights into the decision-making processes in response to safety notices. This qualitative data could complement quantitative findings and provide a more complete understanding of the factors at play.

There is also a need for the development of more advanced analytical models capable of capturing the multi-dimensional nature of market responses to safety notices. Future studies should consider using real-time data integration, such as electronic health records, to observe the impact of safety notices as they occur in clinical practice. Additionally, examining the impact of international regulatory differences on the effectiveness of safety notices through comparative studies could reveal how variations in regulatory frameworks influence their effectiveness.

Further research should also investigate how regulatory bodies can become more proactive in addressing potential issues before they necessitate safety notices. This might involve closer collaboration with scientific and clinical communities and leveraging emerging technologies to predict and mitigate risks earlier in the device lifecycle.

In conclusion, this study has provided insights into the relationship between safety notices and knee implant selection but also highlights significant areas for further research. By addressing these limitations and exploring new avenues of investigation, future studies can develop a more comprehensive understanding of how regulatory actions influence clinical practice. This work will be essential for ensuring that regulatory strategies effectively support patient safety and the responsible use of medical technologies, ultimately leading to better outcomes for patients and more robust healthcare systems.

Code and data

https://github.com/Santonastaso/MSc-TU-Delft-Thesis

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