The regulatory burden of Regulation 2017/745 placed on manufacturers of legacy devices and the potential impact of market shortages as manufacturers strive to comply.

Research Dissertation presented for the degree of Master of Science in Medical Device Technology & Business

STUDENT NAME: Kate Brennan

SUPERVISOR'S NAME: Dr. Gillian McMahon

CANDIDATE DECLARATION

Candidate Name: Kate Brennan

I certify that the dissertation titled:

"The regulatory burden of Regulation 2017/745 placed on manufacturers of legacy devices and the potential impact of market shortages as manufacturers strive to comply" submitted for the degree of MSc in Medical Device Technology & Business is the result of my own work and that where reference is made to the work of others, due acknowledgment is given.

Candidate Name: Kate Brennan
Candidate Signature: Kate Brennan
Date: 16/05/25

Supervisor Name: Gillian McMahon
Supervisor signature: Gillian McMahon
Date: 16/5/24

ABSTRACT

BACKGROUND:

The MDD (Medical Device Directive 93/42/EEC) and AIMD (Active Implantable Medical Device Directive 90/385/EEC) have been repealed and replaced by MDR 2017/745. MDR 2017/745 places a significant regulatory and financial burden on medical device manufacturers as they strive to meet the new requirements. In contrast to the US regulatory scheme there are no provisions for grandfathering products certified under the previous Directives.

The purpose of this research was to identify, define and describe the regulatory burden of Regulation 2017/745 placed on manufacturers of legacy implantable, intra-articular medical devices for treatment of Osteoarthritis and the potential impact of market shortages as manufacturers strive to comply.

Osteoarthritis is a disease occurring mainly in adults over 50 years of age and results in reduced quality of life. Osteoarthritis is a disorder of synovial joints. Some complications of the disease include difficulty walking, performing day-to-day tasks, chronic pain and mental health issues resulting from the physical challenges and pain suffered by patients.

Legacy implantable intra-articular devices such as Durolane®, Hyalgan® and Synvisc® have been available on the European market under the Medical Device Directive 93/42/EEC. Literature indicates the product is a valuable treatment option for patients in terms of efficacy and cost and contribute to an improved quality of life for Osteoarthritis sufferers.

METHODS:

This research explores the difficulties encountered by manufacturers as they strive to comply and also the potential knock-on effect for patients and Health Care Practitioners in the event products are in short supply. Information was collected in the form of a survey and interviews with experts. A questionnaire was developed using Microsoft Teams Form, issued to colleagues, and disseminated via LinkedIn. The data collected is qualitative and quantitative in nature and was analysed using thematic analysis and statistics. The surveys were targeted at professionals within the medical device industry to gather information on how MDR has impacted businesses specifically in clinical evaluation. Semi-structured, recorded interviews were conducted with Clinicians, Pharmacists and Marketing personnel to understand the impact a market shortage would have on patients.

FINDINGS:

Data to comply with MDR clinical requirements is being sourced almost equally from literature searches, clinical investigations, and post market sources. Respondents agree that clinical evaluation requirements are well-expressed in guidance documents. Clinical evidence gathered for devices under MDD is lacking, resulting in revisions to intended purpose, indication statements and associated clinical benefits of the device(s), the conditions of use, specific contraindications, and risk management files. A third of surveyed manufacturers expect a decrease in patients accessing the device and 50% expect a reduction in sales. For patients, a market shortage will impact those who are ineligible for NSAIDs and have exhausted other therapeutic options.

CONCLUSIONS:

As a result of the cost to organisations in terms of resources needed to meet MDR requirements and potential for loss of sales, the MDR places a manufacturer in an unfavourable financial position. Manufacturers may withdraw products from the EU market. The knock-on effect for patients using intra-articular medical devices for Osteoarthritis treatment will be of significance for those who are

ineligible for NSAIDs when physical therapy, basic pharmacological treatment, and first-line joint injection with corticosteroid have not given adequate relief.

MDR may also be presenting a barrier to newer therapies such as PRP, both primary and secondary research has shown that although there is interest from the medical profession, there is little clinical data available.

At the end of the transition period for Class III implantable intra-articular devices, May 2027, we may see a decline in these products available on the EU market and a delay in innovative products reaching the market. Considering the prevalence of OA within society, the impact of the MDR may be significant for patients.

Table of Contents

CANDIDATE DECLARATION 2

ABSTRACT 3

BACKGROUND: 3

METHODS: 3

FINDINGS: 3

CONCLUSIONS: 3

LIST OF FIGURES 7

LIST OF TABLES 7

ABBREVIATIONS 7

APPENDICES 8

CHAPTER 1: INTRODUCTION 9

1.1 THE HISTORY OF EU MEDICAL DEVICE REGULATIONS 9

1.2 HISTORY OF MEDICAL DEVICE REGULATION – US 10

1.3 THE CURRENT REGULATORY FRAMEWORK FOR MEDICAL DEVICES 12

1.4 THE NEW REQUIREMENTS OF MDR 2017/745 COMPARED TO MDD 93/42/EEC 13

1.5 MAJOR CHANGES INTRODUCED IN MDR 2017/745 15

1.6 KEY CHANGES WITH RESPECT TO NOTIFIED BODIES 16

1.7 KEY CHANGES FOR MANUFACTURERS 16

1.8 MDN/ MDT Codes 18

1.9 TYPES OF INTRA-ARTICULAR DEVICES USED FOR TREATMENT OF OSTEOARTHRITIS 20

1.10 CLASSIFICATION OF INTRA-ARTICULAR DEVICES USED FOR TREATMENT OF OSTEOARTHRITIS 22

1.11 SAFETY PROFILE OF INTRA-ARTICULAR MEDICAL DEVICES USED FOR TREATMENT OF OSTEOARTHRITIS 22

1.12 PURPOSE OF THE RESEARCH 24

CHAPTER 2: LITERATURE REVIEW 26

2.1 INTRODUCTION 26

2.2 LEGACY MEDICAL DEVICES AFFECTED BY THE NEW EU REGULATION 27

2.3 DIFFERENCES BETWEEN THE US AND EU REGULATORY APPROACHES TO LEGACY DEVICES 30

2.4 BENEFITS OF THE NEW EU REGULATION MDR 2017/745 32

2.5 AREAS FOR IMPROVEMENT IN EU 33

SUMMARY 35

2.6 REGULATORY TEXTS 36

2.7 ACADEMIC ARTICLES & STUDIES 39

CHAPTER 3: RESEARCH METHODOLOGY 45

3.1 RESEARCH METHOD USED 45

3.2 RESEARCH PHILOSOPHY 46
3.3 RESEARCH APPROACH 46
3.4 RESEARCH STRATEGY 46
3.5 RESEARCH CHOICES 47
3.6 TIME HORIZONS 47
3.7 TECHNIQUES & PROCEDURES 47
3.8 ETHICS CONSIDERATIONS 47
3.9 QUESTIONNAIRE/SURVEY 48
3.10 INTERVIEW 49
CHAPTER 4: FINDINGS AND DISCUSSION 50
4.1 INTRODUCTION 50
4.2 QUESTIONNAIRE 50
4.2.1 DEMOGRAPHIC INFORMATION 50
4.2.2 GENERAL QUESTIONS RELATED TO MDR 52
4.2.3 CLINICAL EVIDENCE QUESTIONS 55
4.2.4 OUTSOURCING OF ACTIVITIES/ BUSINESS IMPACTS 59
4.3 INTERVIEW QUESTIONS 60
4.3.1 DEMOGRAPHIC INFORMATION 60
4.3.2 GENERAL QUESTIONS RELATING TO OSTEOARTHRITIS 60
4.3.3 SPECIFIC QUESTIONS RELATING TO INTRA-ARTICULAR MEDICAL DEVICES 61
4.3.4 QUESTIONS RELATED TO PATIENT IMPACT IN THE EVENT OF MARKET SHORTAGE 64
SUMMARY 65
CHAPTER 5: RESEARCH CONCLUSION 67
RESEARCH CONCLUSIONS 67
5.1 BASED ON THE MAIN RESEARCH OBJECTIVES 67
5.2 RESEARCH LIMITATIONS: 69
5.3 FINAL CONCLUSIONS: 69
5.4 RECOMMENDATIONS 69
REFERENCES AND BIBILIOGRAPHY 71

LIST OF FIGURES

Figure 1 – Illustration of Osteoarthritis progression

Figure 2 - X-rays of Normal and Arthritic Knee joints

Figure 3 - Durolane Medical Device

LIST OF TABLES

Table 1 – KEY MILESTONES IN FDA REGULATION

Table 2 - MDD STRUCTURE VERUS MDR STRUCTURE

Table 3 - MDR STRUCTURE

Table 4 – EUDAMED ACTIVTIES

Table 5 – MDN/MDT CODES

Table 6 – FDA CATEGORISATION

Table 7 - MAUDE DATABASE DATA

Table 8 – GUIDING PRINCIPLES FOR CLINICAL TRIALS

ABBREVIATIONS

AIMD – Active Implantable Medical Device

CE - Conformité Européenne

CER – Clinical Evaluation Report

CIP – Clinical Investigation Plan

CS – Common Specifications

ESCO - European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis

GCP – Good Clinical Practice

GMP – Good Manufacturing Practice

GSPRs - General Safety and Performance Requirements

HA – Hyaluronic Acid

HCP – Healthcare Practitioner

IAHA – Intra-articular Hyaluronic acid

IEC - Independent Ethics Committee

IFU – Instructions for Use

IRB - Institution Review Board

ISO - International Organization for Standardization

MAUDE - Manufacturer and User Facility Device Experience

MDA – Medical Device Active

MDCG – Medical Device Co-Ordination Group

MDD – Medical Device Directive

MDN – Medical Device Non-Active

MDR – Medical Device Regulation

MDS – Medical Device specific characteristics

MDT – Medical Device Technology

MHRA - Medicines and Healthcare products Regulatory Agency

NB – Notified Body

NSAIDs - Non-steroidal anti-inflammatory drugs

OA – Osteoarthritis

PIP - Poly Implant Prothese

PMA – Pre-Market Approval

PRP – Platelet Rich Plasma

QMS – Quality Management System

RCT – Randomised Control Trial

SaMD – Software as a medical device

SSCP - Summary of Safety and Clinical Performance

SYSADOA - Symptomatic slow-acting drugs for OA

UDI – Unique Device Identifier

UDI-DI - Unique Device Identifier – Device Identifier

APPENDICES

APPENDIX 1 – RESEARCH PROPOSAL

APPENDIX 2 – ETHICS APPLICATION

APPENDIX 3 – QUESTIONNAIRE

APPENDIX 4 – INFORMED CONSENT FORM

APPENDIX 5 – PARTICIPANT INFORMATION LETTER

APPENDIX 6 – INTERVIEW QUESTIONS

CHAPTER 1: INTRODUCTION

1.1 THE HISTORY OF EU MEDICAL DEVICE REGULATIONS

According to the European Commission press release of 05 April 2017, there are over half a million types of medical device and in-vitro diagnostic medical devices on the European market. These devices range from breast implants to simple adhesive plasters.

The previous device framework was composed of three Directives dating back to the 1990's. In 1993 the medical device directive EC 93/42/EEC was introduced and appended in 2007 by 2007/47/EC. Issues related to differences in interpretation between member states, technology advancements and scandals such as the PIP breast implant (Poly Implant Prothese) and DePuy Hip replacement implant drove the need to revise the Directives.

The PIP implant scandal is one of the highest profile medical device scandals in history. The scandal broke in 2010 but the MHRA in the UK had been receiving reports of issues with the implants as far back as 2002. A total of 269 incidents were reported to MHRA between 2001 and 2009. The MHRA began notifying the manufacturer of the issues from 2003 and following an inspection of the manufacturer by the French Competent Authority, a ban was placed on PIP implants. The concern of the French Competent Authority was based on use of unapproved filler in the implants. The French Competent Authority recommended removal of PIP implants in all patients as a precaution. According to the British Medical Journal (BMJ 2012;345:e4560), PIP silicone breast implants containing non-medical grade silicone were implanted in approximately 47,000 women in the United Kingdom. The scandal resulted in bankruptcy for the manufacturer Poly Implant Prothèse (PIP) and significant impact to patients' lives.

The DePuy ASR hip replacement implant is another well publicized scandal. A report by the Irish Times (Nov 25, 2018) indicates that at that time upwards of 1,000 Irish patients had issued proceedings against DePuy. It is stated that more of these implants had been used in Irish patients on a per capita basis than in any other market. Patient stories were shared in this article, detailing the impact to patient quality of life. The DePuy ASR implant was a metal-on-metal implant that was promoted as a "game changer" in the field of orthopedics. This device consisted of a ball and cup manufactured from a cobalt chromium metal alloy whereas previous implants were manufactured from a metal ball and plastic cup.

The DePuy ASR products were approved by the UK Notified Body BSI. At the time of certification, clinical trials were not required under the Medical Device Directive. Markets outside of the EU rely on the CE mark as assurance of the product safety. As such, certification by BSI allowed the product to reach other markets. DePuy were granted FDA approval using the substantial equivalence method which allows for approval provided the device is deemed as safe and effective as the predicate device. The predicate devices used by DePuy to gain approval had been withdrawn from the market due to known failures. This shows a massive flaw in this regulatory pathway which is controversial for many reasons.

DePuy's product was recalled from the Irish Market in 2010 and since then many experts have provided their opinions on the device design. According to an Engineering Professor at Trinity College Dublin, David Taylor, the critical error made by DePuy engineers was a failure to test the design prior to implanting in patients. The most serious issues reported by surgeons are ion poisoning, tissue necrosis and early revisions.

It has been reported but not proved that DePuy were aware of the design flaws, particularly with the smaller devices intended for patients with a smaller body frame, prior to placing the product on market. Although these scandals highlight the need for regulatory reform there is also a need for moral responsibility on the part of manufacturers.

Innovation geared towards improvement of patient lives is key, but the regulatory framework must take a balanced approach to ensure the safety and efficacy of these products.

To reform the Directives, the European Commission proposed two new regulations. The main aims of the regulations are to improve market surveillance, enhance traceability of devices and ensure devices are manufactured according to the technological state-of-the-art.

Increased scrutiny and consultation procedures by Notified Bodies for devices prior to placing on market is directed at improving quality, safety and reliability of medical devices. Implants are naturally subject to tighter control. Implants require an implant card to provide patients with safety information and a unique device identifier is required for all products for traceability within the EUDAMED database.

The EUDAMED system is geared towards enhanced market surveillance for manufacturers and regulators.

While the “new” regulatory framework is patient safety focused, it presents many challenges for manufacturers, regulators and medical professionals.

1.2 HISTORY OF MEDICAL DEVICE REGULATION – US

Key milestones in the FDAs regulation of Food and Drugs are stated below.

Table 1 – KEY MILESTONES in FDA REGULATION

Year & Act	Key change
1906: Pure Food and Drugs Act	Introduced prohibition of sale of misbranded or adulterated food and medicines.
1938: Federal Food, Drug, and Cosmetic Act (FD&C Act)	FDA began regulating medical products. Prohibition introduced by Pure Food and Drugs act was extended to medical devices.
1976: Medical Device Amendments to the FD&C Act	Introduction of quality requirements aimed to ensure reasonable safety and effectiveness of medical devices. Introduction of a risk-based classification. Introduction of PMA and 510(k) premarketing pathways. Introduction of regulatory pathway for new devices intended for investigational testing in patients.

	Introduction of post market requirements such as GMPs, establishment registration and reporting of adverse events. The FDA were given authorization to ban medical devices.
1990: Safe Medical Devices Act (SMDA)	Increased post market surveillance activities. Authorisation for FDA to initiate recalls in certain circumstances. Introduction of substantial equivalence through the 510(k) pathway.
1997: Food and Drug Administration Modernization Act (FDAMA)	Introduction of the "least burdensome" approach for review. Allowed for leveraging off studies for older versions of a device for premarket submissions for newer iterations of a device. Introduced the De Novo pathway for lower risk devices.
2002: Medical Device User Fee and Modernization Act (MDUFMA)	Introduction of new requirement for reprocessed devices. Introduction of electronic registration for establishments. Introduction of the Office of Combination Products.
2007: Food and Drug Administration Amendments Act (FDAAA)	Improvements to premarket review times. Introduction of UDI system.
2012: Food and Drug Administration Safety and Innovation Act (FDASIA)	Updated De Novo pathway to direct approach. FDA began working with other regulators to harmonise approach.
2016: 21st Century Cures Act	Introduction of policies to expedite patient access to certain products. Definition of SaMD (software as a medical device).
2017: Food and Drug Administration Reauthorization Act (FDARA)	Introduction of risk-based inspections of manufacturers. Separation of accessories from the parent device – classification FDA began a pilot study to assess value of real-world evidence in PMS.

2020: Coronavirus Aid, Relief, and Economic Security Act (CARES Act)	Improvements to ensure continuity of product supply for related devices.
2022: FDA User Fee Reauthorization Act of 2022 (FDAUFRA)	Improvement to submission process.
2022: Food and Drug Omnibus Reform Act of 2022 (FDORA)	Improved oversight of manufacturers, including remote inspections. Cybersecurity requirements for certain devices. Introduced FDA ability to ban devices for one or more intended use. Enhanced oversight of device establishments, including new authority to conduct remote regulatory audits and to inspect facilities that conduct research on devices.

1.3 THE CURRENT REGULATORY FRAMEWORK FOR MEDICAL DEVICES

The MDD (Medical Device Directive 93/42/EEC) and AIMD (Active Implantable Medical Device Directive 90/385/EEC) have been repealed and replaced by MDR 2017/745.

MDR 2017/745 places a significant regulatory and financial burden on medical device manufacturers as they strive to meet the new requirements. In contrast to the US regulatory scheme there are no provisions for grandfathering products certified under the previous Directives. Grandfathering is a term used to describe medical devices placed on the U.S. market prior to 1976 when the Food and Drug Administration began regulating devices. Before passing of the Medical Device Amendments in 1976 there was no requirement for medical device manufacturers to register their devices with the existing regulatory agency or have any quality standards in place.

It is important to note that no requirements of the previous directives have been removed; the MDR only adds further requirements.

Some of the main changes introduced by the MDR are listed below.

- Classification rules
- Registration of Notified Bodies and Economic Operators

- Introduction of scrutiny procedure for Notified Bodies certifying Class IIb and Class III devices
- Preparation and update of Technical Documentation File in accordance with Annex II
- Introduction of new labelling requirements
- Greater emphasis on Clinical Evaluation and investigations
- Introduction of UDI (Unique Device Identifier)
- Introduction of the EUDAMED system
- Implant Card for certain devices
- Summary of Safety and Clinical Performance (SSCP) required for certain devices

All Class III and implantable devices require clinical data from clinical investigation conducted in accordance with Good Clinical Practice.

Manufacturers operating in the EU must comply with these requirements as ‘grandfathering in’ is not permitted.

Transitional provisions have been set out under Article 120 of MDR 2017/745 to minimise the risk to market supply.

There are conditions that apply to manufacturers holding certificates issued under the directives. The devices certified may only be placed on the market during the transitional period provided there are no significant changes made to the product intended purpose of design. MDR requirements related to PMS, vigilance, market surveillance, registration of economic operators in EUDAMED and device registration applies.

MDCG Guidance Document 2021-25, (Regulation (EU) 2017/745 – Application of MDR requirements to legacy devices and devices placed on the market prior to 26 May 2021 in accordance with Directives 90/385/EEC or 93/42/EEC), outlines requirements pertinent to legacy devices. This document defines legacy devices as those placed on the market before 26 May 2021 under the directives. Some of the key requirements for legacy devices are updates to PMS (Post-Market Surveillance) and vigilance requirements, transitional surveillance activities for Notified Bodies and update to Periodic Safety Update Report Requirements.

In addition to highlighting applicable MDR requirements the document also highlights non-applicable requirements.

1.4 THE NEW REQUIREMENTS OF MDR 2017/745 COMPARED TO MDD 93/42/EEC

It is important to note that MDR does not remove requirements of MDD; the MDR only adds further requirements. At a cursory glance, the MDR is significantly longer and prescriptive than the MDD.

Table 2 below gives a comparison of the two regulatory texts.

Table 2 - MDD Structure versus MDR Structure

MDD 93/42/EEC	MDR 2017/ 745
23 Articles	123 Articles
12 Annexes	17 Annexes
18 Rules	22 Rules
60 Pages	175 Pages

The MDR structure is detailed in the table below.

Table 3 - MDR Structure

Chapter/ Annex	**MDR Content**	**Articles**
Chapter I	Scope and definitions	1 to 4
Chapter II	Making devices available in the market and putting them into service, obligations of economic operators, reprocessing, CE marking, free movement	5 to 24
Chapter III	Identification and traceability of devices, registration of devices and of economic operators, summary of safety and clinical performance, European database on medical devices	25 to 34
Chapter IV	Notified bodies	35 to 50
Chapter V	Classification and conformity assessment	51 to 60
Chapter VI	Clinical evaluation and clinical investigations	61 to 82
Chapter VII	Post-market surveillance, vigilance and market surveillance	83 to 100
Chapter VIII	Cooperation between Member States, Medical Device Coordination Group, expert laboratories, expert panels and device registers	101 to 108
Chapter IX	Confidentiality, data protection, funding and penalties	109 to 113
Chapter X	Final provisions	114 to 123
Annex I	General safety and performance requirements	/
Annex II	Technical documentation	/
Annex III	Technical documentation on post-market surveillance	/
Annex IV	EU declaration of conformity	/
Annex V	CE marking of conformity	/

Annex VI	Information to be submitted upon the registration of devices and economic operators in accordance with articles 29(4) and 31, core data elements to be provided to the UDI database, together with the UDI-DI in accordance with articles 28 and 29, and the UDI system	/
Annex VII	Requirements to be met by notified bodies	/
Annex VIII	Classification rules	/
Annex IX	Conformity assessment based on quality management system and on assessment of technical documentation	/
Annex X	Conformity assessment based on type-examination	/
Annex XI	Conformity assessment based on product conformity verification	/
Annex XII	Certificates issued by a notified body	/
Annex XIII	Procedure for custom-made devices	/
Annex XIV	Clinical evaluation and post-market clinical follow-up	/
Annex XV	Clinical investigations	/
Annex XVI	List of groups of products without an intended medical purpose referred to in article 1(2)	/
Annex XVII	Correlation table	/

1.5 MAJOR CHANGES INTRODUCED IN MDR 2017/745

Key changes are as follows:

- Classification Rules
- Registration of Notified Bodies and Economic Operators within the EUDAMED database
- Introduction of scrutiny procedure for Notified Bodies certifying Class IIb and Class III devices
- Preparation and update of Technical Documentation File in accordance with Annex II
- Introduction of new labelling requirements
- Greater emphasis on Clinical Evaluation and investigations
- Introduction of UDI (Unique Device Identifier)
- Introduction of the EUDAMED system
- Implant Card for certain devices
- Summary of Safety and Clinical Performance (SSCP) required for certain devices

An extended transitional period has been granted for legacy devices. Legacy device manufacturers can utilize the extended transitional period provided certain conditions (Article 120 (c)) are met. MDD certificates that were valid on the MDR's date of application (26 May 2021) are automatically extended provided the manufacturer has entered into an agreement with a Notified Body for conformity assessment of the device.

1.6 KEY CHANGES WITH RESPECT TO NOTIFIED BODIES

1. Under MDR, Notified Bodies (NBs) must be designated under the regulation in order to carry out conformity assessment of medical devices. This requires application by Notified Bodies for assessment. Designation of the Notified Body is granted by Member States. Upon Notified Body fulfilment of the relevant requirements, the Member State is responsible for informing the Commission and other Member States that the NB has been designated to conduct conformity assessment under the Regulation. According to European Commission Single Market Compliance Space there are 43 NBs designated under MDR. Under MDD 93/42/EEC there were 50 NBs designated. Not all MDD designated NBs have been granted or applied for designation under MDR which can result in a challenge for a manufacturer where they need to change their NB in order to retain their product on market.
   The new requirements are burdensome for NBs, requiring longer review times which means NBs will struggle to take on new clients and products.

2. Scrutiny Procedure applies to devices deemed to have a higher risk. This new procedure may delay launch of products. Under this procedure the NB must prepare an assessment of the Clinical Evaluation for review by an expert panel of the European Commission. The expert panel must provide scientific opinion within 60 days of submission by the NB. The expert panel may either raise questions that must be addressed or state non-consideration. Legacy devices are subject to exemption from this procedure provided no design changes have been made to the device since last MDD certification. This also places a manufacturer in an unfavourable position as they essentially face a design-freeze during the MDR transition period.

1.7 KEY CHANGES FOR MANUFACTURERS

1. Changes in Classification Rules. Under MDR framework medical devices are classed as I, IIa, IIb and III. Classification is risk based and dependent on the nature of the contact between the device and the user, class I is the lowest risk class while III is the highest. There are 22 classification rules under MDR on comparison to 18 classification rules under MDD. The classification rules are more stringent resulting in some devices being reclassified to a higher risk class.

2. Additional requirements for demonstration of Clinical Evidence. Clinical Evaluation reports were required under MDD but additional requirements for Clinical Evaluation reports have been included in MDR. Class III and implantable devices now require clinical data sourced from a clinical study in accordance with Article 2. Supporting MDCG Guidelines such as MDCG 2020-5 and 2020-6, are designed to provide a framework for manufacturers to establish clinical evidence. All devices, irrespective of class must comply with the General Safety and Performance Requirements. There are some exemptions such as changes to existing devices,

equivalence to an already CE marked device (under MDR) and MDD certification of the device with sufficient clinical data to meet MDR requirements. Class III and certain Class IIb must also follow the clinical evaluation consultation procedure. Under Article 54(2) of the MDR, there are criteria that exempt devices from this procedure. The article states that: “The procedure referred to in paragraph 1 shall not be required for the devices referred to therein: (a) in the case of renewal of a certificate issued under this Regulation; (b) where the device has been designed by modifying a device already marketed by the same manufacturer for the same intended purpose, provided that the manufacturer has demonstrated to the satisfaction of the notified body that the modifications do not adversely affect the benefit-risk ratio of the device; or (c) where the principles of the clinical evaluation of the device type or category have been addressed in a CS (Common Specification) referred to in Article 9 and the notified body confirms that the clinical evaluation of the manufacturer for this device is in compliance with the relevant CS for clinical evaluation of that kind of device”.

3. Summary of Safety and Clinical Performance (Article 32). The SSCP is required for certain classes of devices. The SSCP will be uploaded to the EUDAMED website following approval of the content by the NB. MDR mandates that manufacturers of Class III and implantable devices (excluding custom made and investigational devices) prepare a SSCP which requires validation of the content by the Notified body prior to uploading to the EUDAMED database. The SSCP once uploaded to the EUDAMED database will be accessible by the public. The purpose of the SSCP is to make relevant clinical and device performance information available for both the Healthcare Professional and the patient. The SSCP will enhance the availability of information for both users and recipients of devices. The SSCP also contains information needed to improve traceability of the device in the event of an adverse reaction.

4. Unique Device Identification (UDI) Numbers. The UDI system is a barcoding system intended to improve traceability of devices, improve vigilance and also provide greater oversight to Competent Authorities. The information contained within the barcode must also be present in human readable form and the manufacturer is responsible for maintaining the list of UDIs. The manufacturer is also responsible for considering if a new UDI-DI (UDI Device Identifier) is required in the course of device changes. For example, a change in sterilisation method would trigger need for a new UDI-DI to avoid misidentification of the device.

5. EUDAMED Database. Many articles in MDR detail requirements for registration of information electronically in the EUDAMED database. This database is a web-based portal with access for Economic operators, the public and also regulatory agencies. An update on EUDAMED modules was issued in February 2024 following the European Commission proposal to delay the IVDR compliance deadline. The proposal states that the EUDAMED modules will become mandatory before all modules have been validated.

   There are six modules:

   1. UDI/Devices
   2. Actors
   3. Notified bodies/Certificates
   4. Post-Market Surveillance and Vigilance
   5. Market Surveillance

6. Clinical Investigations/Performance Studies

Modules 1, 2 and 3 have already been made available for voluntary use.

The module on Market Surveillance (for member state use only) and the module on PMS and Vigilance are expected to be completed in Q2 of 2024. The EC does not expect the module on Clinical Investigations and Performance Studies to go live before Q3 of 2026. If the modules are made mandatory, industry will have six months from the date of publication in the Official Journal of the European Union to comply.

The European Commission document dated 15 Dec 2022, Functional specifications for the European Database on Medical Devices (EUDAMED) - to be audited (only for Minimum Viable Product (MVP) Legal Priority), describes the roles and functionality of the EUDAMED system.

Within the restricted module for Clinical Investigations/Performance the following activities are relevant.

Table 4 – EUDAMED ACTIVTIES

Responsible Party	Action
Sponsor	• Submission of application for Clinical Investigation/ Performance Studies • Notify Concerned Member States of studies and any modifications • Timely response to application queries from Member states • Notify Concerned Member States in the event of termination, pause or completion of studies • Report findings of studies to Concerned Member States including any adverse event and device deficiencies • Notify Member States of completion of the studies • Submit study outcome report with its summary
Competent Authority	• Notify sponsor of acceptance or rejection of application and advise of required timelines • Permit additional time for the sponsor to respond to application questions • Notify the Sponsor of the Central Member State • Coordinate Member States assessment of application • Monitor the studies
Commission	• Manage the database
Public	• Access summary reports made available within the database

1.8 MDN/ MDT Codes

MDCG 2019-14 Explanatory Note on MDR Codes provides guidance on the application of MDR medical device codes. The purpose of the codes is to define the scope of the notified body designation

(assessor qualifications) but they also are used to characterise devices by their design, materials, intended purpose, method of manufacturing and technologies involved.

MDA / MDN Codes are used to categorise the design and intended use. The 'A' denotes active device and the 'N' denotes non-active. One code is selected per device. MDS codes categorise the characteristics of the device and MDT codes categorise the technology and processes linked to the device. For both MDS and MDT codes multiple selections are possible.

Intra-articular medical devices for treatment of Osteoarthritis can be categorised as follows:

Table 5 – MDN/MDT CODES

MDN Code	**MDN 1102 - Non-active osteo- and orthopaedic implants**
MDS Code	MDS 1003 - Devices manufactured utilising tissues or cells of animal origin, or their derivatives (code is pertinent to sodium hyaluronate raw material sourced from bacterial fermentation) MDS 1005 - Devices in sterile condition
MDT Code	MDT 2008 - Devices manufactured in clean rooms and associated controlled environments

These categorisation codes are of interest as they could be used to categorise devices for the purpose of data sharing/ gathering by manufacturers. Their use could be extended from use by regulators to collaboration by manufacturers of devices within the same category.

During my research, I contacted EUDAMED highlighting the potential for the Clinical Investigations/Performance Studies module within EUDAMED to allow manufacturers of similar devices (on mutual agreement) to share clinical data and studies based on the MDR coding system.

The response received by EUDAMED was as follows:

The use of the Clinical Investigations and Performance Studies module is mostly meant for the use of Competent Authorities and Sponsors. At the current state there is no direct way to share this kind of information within EUDAMED. Please note that the database is not functional yet so it is subject to change.

The FDA classify intra-articular medical devices for OA treatment under the following category –

Table 6 – FDA CATEGORISATION

Device	**Acid, Hyaluronic, Intraarticular**
Review Panel	Orthopedic
Product Code	MOZ

The FDA Database Total Product Life Cycle provides information on this category of device under the following topics:

- PMA (Pre-Market Approvals)
- Medical Device Reports
- Device Problems
- Patient Problems

Using the FDA database, it is possible to also review PMA documents issued by the FDA which would be an invaluable resource if a similar database was created within the EU.

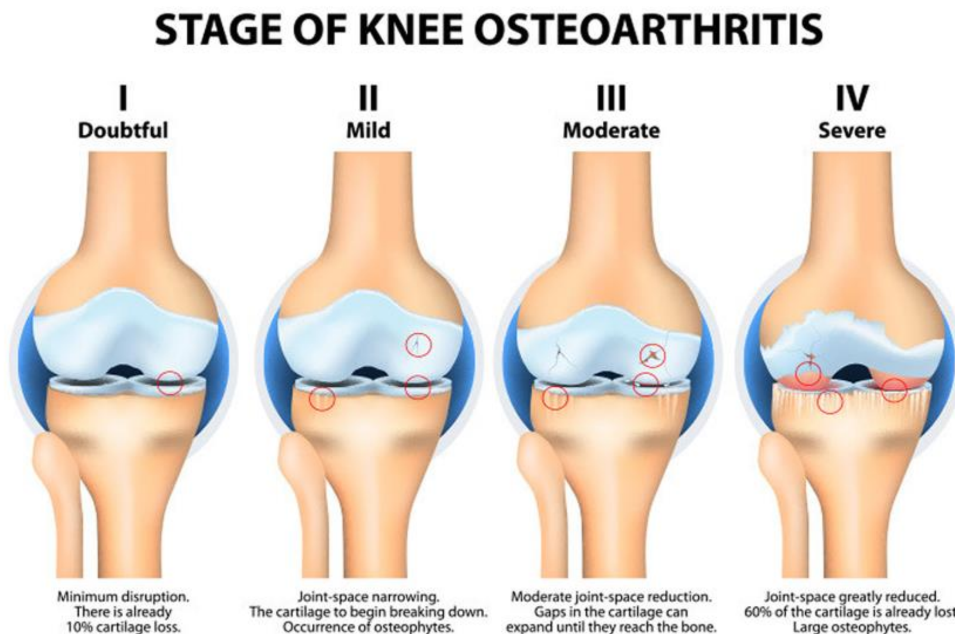
1.9 TYPES OF INTRA-ARTICULAR DEVICES USED FOR TREATMENT OF OSTEOARTHRITIS

Osteoarthritis is a disease occurring mainly in adults over 50/60 years of age and is more common in women, pre-dominantly post-menopausal women. OA is progressive and results in reduced quality of life. World Health Organization defines "quality of life" as a person's perception of his/ her position in life in the context of the culture and value systems in which he lives and in relation to his goals, expectations, standards, and concerns.

According to Kawano et.al., (2015), musculoskeletal diseases are one of the most prevalent conditions across the globe. Osteoarthritis is a progressive chronic condition characterized by deterioration of articular cartilage.

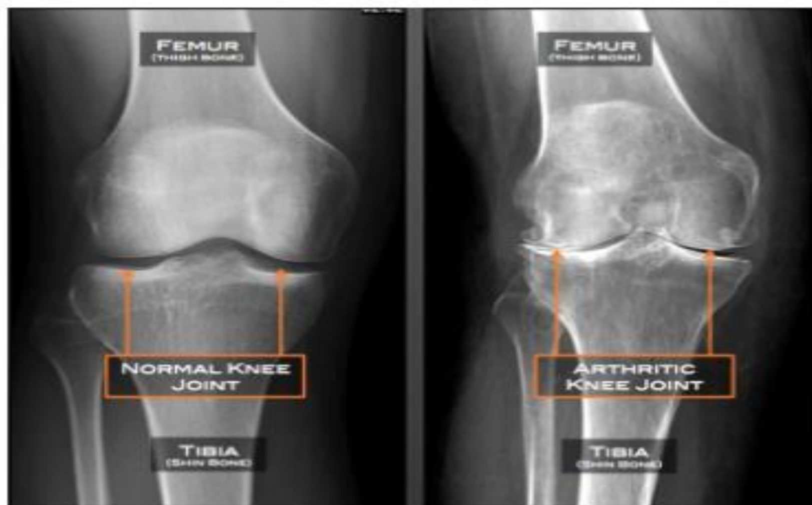
Some complications of the disease include difficulty walking, performing day-to-day tasks, chronic pain, stiffness, difficulty sleeping and mental health issues resulting from the physical challenges and pain suffered by patients. In younger sufferers, it may impair a person's ability to work.

Figure 1 – Illustration of Osteoarthritis progression



Source: *Osteoarthritis - Causes, Symptoms, Diagnosis, Prognosis & Treatment (healthjade.com)*

Figure 2 - X-rays of Normal and Arthritic Knee joints



Source: *Osteoarthritis - Causes, Symptoms, Diagnosis, Prognosis & Treatment (healthjade.com)*

The disease results in reduced function in the affected joint, pain, stiffness, and an overall diminished quality of life for patients. As the patient experiences more pain and stiffness, their willingness to move decreases. With disease progression there is a snowball effect for the patient, increased challenges in daily activities can contribute to other issues such as loss of earnings, diminished social life, mental health problems, relationship problems, stress and difficulty sleeping.

Legacy implantable intra-articular devices such as Durolane®, Hyalgan® and Synvisc® have been available on the European market under the Medical Device Directive 93/42/EEC. Additionally, these devices have been available on the US market for many years and according to the FDA PMA Database, Durolane and Synvisc were granted PMA approval in 2017. These products are all similar, provided as a pre-filled syringe containing sodium hyaluronate. Use of the device is simple, the physician removes the luer tip, attaches a suitable sterilised needle and injects into the intra-articular space in the knee joint.

Figure 3: Durolane Medical Device

These devices play a role in improving QoL of Osteoarthritis sufferers. Viscosupplementation (injection of hyaluronic acid into the intra-articular space in affected joints) is recommended for patient with symptomatic mild to moderate Osteoarthritis who have not benefited sufficiently from non-pharmacological treatment and analgesics/ NSAIDs or are unable to take analgesics/ NSAIDs.

1.10 CLASSIFICATION OF INTRA-ARTICULAR DEVICES USED FOR TREATMENT OF OSTEOARTHRITIS

The classification of intra-articular devices for OA as a medical device is consistent with the definition of a medical device in EU MDR Article 2 (1) as they are a "medical device"….. intended by the manufacturer to be used for human beings for the purpose of:

— treatment or alleviation of disease, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

Section 1.2.4 of MDCG 2022-5 – "Guidance on borderline between medical devices and medicinal products under Regulation (EU) 2017/745 on medical devices" presents a decision tree for determining if a product fulfils the definition of medical device, taking into consideration the intended use, the intended action, and the specific medical purpose of the product. Both medical devices and medicinal products may be intended to treat or prevent disease; the guidance identifies that the "principal mode of action" is the key factor for distinguishing between a medical device and a medicinal product.

These devices are totally introduced into the human body through clinical intervention. The primary mode of action is mechanical; injection of exogenous HA into the affected joint results in increased viscoelasticity of the synovial fluid providing improved shock absorption and lubrication during movement of the joint allowing greater movement with less pain. The shock absorption during movement may be described as a "cushion effect" providing greater comfort for the patient and improving the patient quality of life. As a patient feels more comfortable, mobility is improved. Secondary actions following absorption of the injected HA include restoration of metabolic and rheological homeostasis of the synovial fluid and stimulation of endogenous HA biosynthesis by synovial fibroblast. This results in increased joint mobility due to pain relief.

As these products do not achieve their principal intended action by pharmacological, immunological or metabolic means they are considered a medical device under the definition of the EU MDR and MDCG 2022-5.

1.11 SAFETY PROFILE OF INTRA-ARTICULAR MEDICAL DEVICES USED FOR TREATMENT OF OSTEOARTHRITIS

According to Maheu et.al, (2015), ESCO (European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis) recommends use of intra-articular injections for OA treatment in patients suffering with knee OA who have not responded to non-steroidal anti-inflammatory drugs. The basis of the recommendation is the evidence that these medical devices increase joint mobility, decrease pain and the resultant improvements are longer lasting than that of intra-articular corticosteroids. According to this article these medical devices are considered safe although the article

does report that there is a higher incidence of post-injection non-septic arthritis with higher molecular weight cross-linked preparations.

For this research, the FDA Adverse Event Maude Database was reviewed for the purpose of confirming the safety of these devices. The MAUDE database was selected for review as it is most accessible. The search criteria used was the product brand name and the classification code MOZ which relates to Acid, Hyaluronic, Intraarticular.

The following data was retrieved from the database.

Table 7 - MAUDE DATABASE DATA

Product	Number of Adverse events (01/01/2023-31/12/23)	Nature of reports
Durolane	24	Defective product, device malfunction, post-injection flare such as stiffness, pain and hypersensitivity. Two reported deaths listed in the database but not attributed to device use.
Hyalgan	2	1 report of anaphylactic shock in a patient with multiple allergies. 1 report of allergy.
Synvisc	146	Of the reported cases, 14 were listed as reports of deaths. 10/14 were reported with no cause of death provided and 4/14 the cause of death was cancer. All other cases were linked to defective product, device malfunction, post-injection flare such as stiffness, pain and hypersensitivity.

A review of the Instructions for Use for each product indicates that the adverse events reported in the MAUDE database are well documented and are highlighted to the user. According to the Hyalgan IFU there have been 50 million injections administered since launch in 1987. Transient local reactions such as pain and swelling are known for this product.

According to the Durolane Instructions for Use, known adverse reactions are given as transient pain, swelling and/or stiffness localized to the joint. No other reported adverse events have been classified as acute inflammatory arthritis or allergic reactions and did not require medical attention.

According to the Synvisc Instructions for Use known adverse events include pain, swelling and/ or effusion. These events are transient in nature. Hypersensitivity including anaphylactic shock is listed as a potential side effect.

The review of the MAUDE database confirms the safety of the devices, the side effects associated are predominantly transient and localized in nature. This further supports a well-documented safety profile of the devices; the manufacturers have many years of market experience and disclose the risks to users.

1.12 PURPOSE OF THE RESEARCH

The aim of this study is to identify specific barriers to MDR (Medical Device Regulation 2017/745) certification for manufacturers of intra-articular devices used to treat Osteoarthritis and evaluate the impact on patient quality of life in the event manufacturers cannot meet the new requirements.

The objectives of this study are as follows:

1. Examine key MDR 2017/ 745 compliance challenges for legacy devices, in particular, the impact of MDR clinical evidence requirements.

2. Compare current EU MDR 2017/745 framework versus US medical device regulatory framework and pharmaceutical product requirements with respect to clinical data.

3. Discover potential patient impact in the event of market shortage for implantable, intra-articular medical devices.

4. Propose possible routes forward for industry and regulators to ensure continuity of supply of implantable, intra-articular medical devices.

The objectives of this study are SMART and are described below:

Specific – The aim of this study is to identify specific barriers to MDR (Medical Device Regulation 2017/745) certification for manufacturers of intra-articular devices used to treat Osteoarthritis and evaluate the impact on patient quality of life in the event manufacturers cannot meet the new requirements.

Measurable- Primary and Secondary research will be conducted to gauge the impact of the regulation. Secondary research will be gathered in the form of literature reviews and primary research will be gathered through questionnaires and interviews.

Attainable- Through targeting specific groups of professionals the objectives can be met.

Relevant- The transition from MDD to MDR is on-going so the research is well timed. The research aims at identifying the specific barrier to MDR certification faced by manufacturers today and the knock-on effect for patient care in the event of market shortage.

Time - This research will take approximately 4 months to complete.

The following sections of this Dissertation cover the following areas –

Chapter 2: Literature Review
In this chapter secondary data is reviewed to determine gaps in current literature which will frame the research objectives.

Chapter 3: Research Methods
This chapter describes the research process of defining the research problem. This chapter discusses the research philosophy, research approach, research strategy, methods chosen, time horizons and technique using the research onion described by Saunders *et al.* (2007) as a guide.

Chapter 4: Findings and Discussion

In this chapter the findings from primary data collection are discussed and analysed. Primary data was collected in two forms, a questionnaire aimed and professionals within the medical device sector with experience in the challenges presented by MDR 2017/745 and through interviews with Clinical and Sales and Marketing experts to fully assess the value of the products in terms of patient QoL and the patient impact in the event of a market shortage. Data is presented in tabular and graphical form to ensure ease of interpretation of the data.

Chapter 5: Research Conclusions

This chapter presents the research conclusions as they relate to the research objectives and recommendations.

CHAPTER 2: LITERATURE REVIEW

2.1 INTRODUCTION

According to the Journal of Managed Care & Specialty Pharmacy, Vol. 24, 2018, osteoarthritis often occurs in adults over 50 years of age and results in disability and reduced quality of life. OA is a disorder of the synovial joints, characterized by damage to the articular cartilage. Incidence of OA has increased in recent years as a result of an ageing population and increased rates of obesity.

Complications of OA may include impairment and disability (difficulty walking, climbing stairs, dressing, driving), inability to perform work tasks (occupational impact), falls, chronic pain and mental health impacts such as anxiety, depression, and sleep issues.

There are currently many intra-articular sodium hyaluronate medical devices available on the European market. These devices face a transitionary period from the MDD to MDR with many challenges that impact both industry and patients.

According to Bowden et al., (2017) nonsteroidal anti-inflammatory drugs (NSAIDs) are often used as a long-term treatment option for Osteoarthritis. This study refers to investigations that conclude HA is as effective as NSAIDs for management of OA pain. This study concludes that HA is a viable option for patients who are ineligible for NSAIDs as a result of the potential for adverse events associated with NSAIDs. This highlights the value of these medical devices for OA sufferers who are not eligible for NSAIDs.

MDR 2017/745 places a significant regulatory and financial burden on medical device manufacturers as they strive to meet the new requirements. In contrast to the US regulatory scheme there are no provisions for grandfathering products certified under the previous Directives.

It is important to note that no requirements of the previous directives have been removed; the MDR only adds further requirements.

Although the requirement for clinical evidence is not new, the MDR introduces the term 'clinical data' in Article 2 (48).

'Clinical data' means information concerning safety or performance that is generated from the use of a device and is sourced from the following:

— *clinical investigation(s) of the device concerned,*

— *clinical investigation(s) or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated,*

— *reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated,*

— *clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up;*

Guidance documents MDCG 2020-5 (Guidance on clinical evaluation – Equivalence) and MDCG 2020-6 (Guidance on sufficient clinical evidence for legacy devices) indicate that the clinical evaluation must show, through scientifically sound and objective evidence that the device meets its intended use, has clinical benefit and that the benefit-risk ratio when compared to other options is acceptable. For Class III devices a Clinical Evaluation Report (CER) is still required but the requirements for the content of these reports have changed. According to Part A of Annex XIV

(Clinical Evaluation) manufacturers must, plan, conduct and document clinical evaluations on a continuous basis.

MDR Article 61(1) states: *Confirmation of conformity with relevant general safety and performance requirements set out in Annex I under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit-risk ratio referred to in Sections 1 and 8 of Annex I, shall be based on clinical data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III. The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose. To that end, manufacturers shall plan, conduct and document a clinical evaluation in accordance with this Article and Part A of Annex XIV.*

All Class III and implantable devices require clinical data from clinical investigation conducted in accordance with Good Clinical Practice.

Manufacturers operating in the EU must comply with these requirements as 'grandfathering in' is not permitted.

Transitional provisions have been set out under Article 120 of MDR 2017/745 to minimise the risk to market supply.

In summary, Article 120 states the following with respect to certification of legacy devices.

All certificates issued prior to 25/05/17 in accordance with Directives 90/385/EEC and 93/42/EEC will remain valid until the expiry date of the certificate; this period cannot exceed a maximum of five years. The exception to this is certificates issued in accordance with Annex 4 and Annex IV of Directive 90/385/EEC or Directive 93/42/EEC respectively - these certificates will expire on 27/05/22 at the latest.

There are conditions that apply to manufacturers holding certificates issued under the regulation. The devices certified may only be placed on the market during the transitional period provided there are no significant changes made to the product intended purpose of design. MDR requirements related to PMS, vigilance, market surveillance, registration of economic operators in EUDAMED and also device registration applies.

MDCG Guidance Document 2021-25, (Regulation (EU) 2017/745 – Application of MDR requirements to legacy devices and devices placed on the market prior to 26 May 2021 in accordance with Directives 90/385/EEC or 93/42/EEC), outlines requirements pertinent to legacy devices. This document defines legacy devices as those placed on the market before 26 May 2021 under the directives. Key MDR requirements relevant to legacy devices are discussed in this document.

In addition to highlighting applicable MDR requirements the document also highlights non-applicable requirements.

2.2 LEGACY MEDICAL DEVICES AFFECTED BY THE NEW EU REGULATION

A potential gap from reviewing current literature is the lack of guidance and regulation for specific groups of legacy devices, particularly in the area of clinical evidence. Legacy devices are medical devices covered by a valid certificate under the existing Directives and can continue to be placed on the market after the date of application of the incoming MDR or IVDR. The definition of a legacy

device applies to general medical devices, active implantable medical devices (AIMDs), and *in vitro* diagnostic medical devices (IVDs).

Although guidance is available for legacy devices, there is no specific guidance for product groups that have been on the market for many years with little or no evolution in their design. Due to their existence in the market for a long period, the manufacturers have a significant amount of data pertaining to safety from the market. Article 54(2) of the MDR lays down three criteria that exempts devices from the pre-market clinical evaluation consultation procedure with the involvement of expert panels. In particular that article states that: "The procedure referred to in paragraph 1 shall not be required for the devices referred to therein: (a) in the case of renewal of a certificate issued under this Regulation; (b) where the device has been designed by modifying a device already marketed by the same manufacturer for the same intended purpose, provided that the manufacturer has demonstrated to the satisfaction of the notified body that the modifications do not adversely affect the benefit-risk ratio of the device; or (c) where the principles of the clinical evaluation of the device type or category have been addressed in a CS referred to in Article 9 and the notified body confirms that the clinical evaluation of the manufacturer for this device is in compliance with the relevant CS for clinical evaluation of that kind of device".

According to Migliore et. al., (2016), there are several IA preparations currently available on the European market - Artz®, Durolane®, Hyalgan®, Hymovis®, Ostenil®, Synvisc®, and Synvisc-One®. Studies by Pavone et. al., (2021), and Billesberger et. al., (2020) support hyaluronic acid based, intra-articular devices in OA management. These devices contribute to improving the quality of life of Osteoarthritis sufferers, but manufacturers may not have sufficient clinical data to support the General Safety and Performance Requirements of MDR 2017/745.

Medical Device Co-ordination Groups have published guidance documents to assist manufacturers, but a common theme can be seen upon review of these documents, a lack of guidance on how manufacturers can collect sufficient clinical evidence.

MDCG 2020-6 (2020), provides a framework for manufacturers to prepare a clinical evaluation. Although the document highlights the GSPRs (General Safety and Performance Requirements) and clinical data required it is limited as it does not provide guidance on the methodology that should be used to collect sufficient clinical evidence. It is also limited as it does not provide guidance for different classes of device or technology groups.

MDCG 2021-6 (2020), highlights the process for conducting a clinical investigation but does not provide a methodology that should be used to collect sufficient clinical evidence.

This finding is further supported by Kearney & McDermott (2023), who conclude that the greatest challenge to manufacturers is determining the volume of data required to demonstrate sufficient clinical evidence. The study identifies the lack of literature published in relation to MDR clinical evaluation. The study by Kearney & McDermott highlights the challenge for manufacturers in terms of clinical evidence but is lacking in what that challenge means for the patient, this research aims to determine the impact to patients in the event of lack of supply and seeks to determine if based on available clinical evidence there may be a reduction in the patients accessing a device.

The lack of guidance for manufacturers around clinical evaluation gives rise to questions 13-19 in the research questionnaire.

MDCG 2020-5 Clinical Evaluation - Equivalence A guide for manufacturers and notified bodies provides guidance for manufacturers who seek to utilize clinical data from an equivalent device under MDR. Equivalence is a not new topic under MDR, it was permitted under MDD and described in MEDDEV 2.7/1 rev. 4. MDCG 2020-5 highlights the new requirements laid out by MDR. In the absence of a clinical investigation, a manufacturer may use clinical data from another device. To claim equivalence a manufacturer must take into consideration the technical, biological and clinical characteristics of the devices.

Technical characteristics relate the device design, conditions of use, physicochemical properties, and specifications. Biological characteristics relate to the substance in contact with the body, the duration of use and characterization of the substances in accordance with the ISO 10993 series. Clinical characteristics refers to clinical application of the device, disease stage to be treated, method of administration, patient profile, and user. Under MDR, the user is of paramount importance as the user plays a role on safety and performance of the device. It is permitted to use more than one device as an equivalent device but all three characteristics must be considered for each device, this stipulation ensures no “cherry-picking” of data.

Although it is possible to use clinical investigation data from another device to support the clinical evaluation, the MDR requirements present a challenge to do so.

There are specific requirements laid out in MDR for manufacturers of Class III and implantable devices claiming equivalence to a device not manufactured by him. In addition to the requirements given in MDR Article 61(4), there must be a legal contract in place allowing the manufacturer access to all design and technical documents. All data, irrespective of whether it is favourable or not, must be included. The leveraged clinical data must have been generated in accordance with MDR requirements. This means the equivalence cannot be claimed for a device that is certified under MDD. The obligation for a legal contract acts as a barrier for manufacturers seeking to claim equivalence as this activity presents significant cost.

Maresova et. al., (2020) determines that EU regulation has led to reduced patent activity in the Czech Republic. In contrast, there has been no decline in patent activity in the US. This information is valuable as it points to EU regulation being a barrier to innovation, this is not necessarily the case in the US. The struggles faced by legacy device manufacturers seems to be comparable to that of innovative firms. It also highlights a larger problem, if legacy device manufacturers are unable to comply with MDR and innovative products cannot reach the market, patient options become extremely limited.

This topic gives rise to a number of the questions in directed at Clinicians & Sales and Marketing experts in the interview part of the research.

Studies by Pavone et. al., (2021), and Billesberger et. al., (2020) support and re-inforce the need for HA injections for OA management. Rosen et. al., (2020) confirms High Molecular Weight HA is cost effective in treating patients with mild to moderate OA, this supports the products as an effective treatment option. Billesberger et. al., (2020) concludes that although PRP (platelet rich plasma) therapy is beginning to replace HA injections and corticosteroids, larger trials are required to confirm the safety and efficacy of this treatment. Based on the findings of Maresova et. al., (2020), innovators in the PRP field may struggle to place PRP products on the market under the MDR.

An interesting point is raised by Migliore et. al., (2016). Through extensive literature review they determined that ‘already on market’ products, which are legacy devices, are lacking in clinical

evidence. The study recommends brand-specific studies to aid clinician decision-making. This study also raises the question of clinician understanding of these products and confidence in these products. This question will be incorporated into the primary data collection (interviews) for this dissertation.

On 23/01/24 the European Commission proposed that all EUDAMED modules will become mandatory before all modules have been validated.

There are six EUDAMED modules:

1. UDI/Devices
2. Actors
3. Notified bodies/Certificates
4. Post-Market Surveillance and Vigilance
5. Market Surveillance
6. Clinical Investigations/Performance Studies

Modules 1, 2 and 3 have already been made available for voluntary use by economic operators. The module on Market Surveillance (for member state use only) and the module on PMS and Vigilance are expected to be completed in Q2 of 2024. The EC does not expect the module on Clinical Investigations and Performance Studies to go live before Q3 of 2026. If the modules are made mandatory, economic operators have 6 months from the date of publication in the Official Journal of the European Union to comply.

Regulation (EU) 2017/745 became effective in the European Union on May 26, 2021. The regulation replaced the previous Directive (93/42/EEC and 90/385/EEC) and placed new responsibility for particular classes of products on the European Medicines Agency and Competent Authorities. The regulation was adopted in April 2017 and the transition period varies by class of product, Class III products such as intra-articular hyaluronic products have until May 2027 to transition provided certain caveats are met. Manufacturers of devices are permitted to place the CE mark (Conformité Européenne) once they have passed conformity assessment. This process includes audit of the QMS (Quality Management System and the Technical Documentation File for the product. Notified Bodies are appointed by the EU Member States to conduct the conformity assessments. In the case of some high-risk devices the Notified Body must gain assessment from expert panels prior to issuing certification. There are also situations in which the Notified Body must gain scientific opinion from the European Medicines Agency prior to issuing certification.

It is well understood that complying with a new regulation will be labour intensive and costly for any organization. Question 20 of the questionnaire seeks to understand the activities outsourced by organizations to comply with MDR 2017/745.

2.3 DIFFERENCES BETWEEN THE US AND EU REGULATORY APPROACHES TO LEGACY DEVICES

In contrast with the transition to MDR in Europe, the U.S. FDA made provisions for “grandfathering” of medical devices in the 1970’s. Grandfathering is a term used to describe medical devices placed on the U.S. market prior to 1976 when the Food and Drug Administration began regulating devices.

Before passing of the Medical Device Amendments in 1976 there was no requirement for medical device manufacturers to register their devices with the existing regulatory agency or have any quality standards in place.

In 1976, the FDA introduced a risk-based classification for medical devices. Grandfathering was intended to ensure continuity of supply of devices to patients, in particular lifesaving devices. All devices placed on market prior to 1976 automatically were classified as medium risk until such time the FDA had an opportunity to review these devices. This system was flawed in that there were countless devices for the FDA to review. These devices, including implantable devices were allowed to be marketed for many years without any scrutiny or studies into their safety and effectiveness.

A well-known product that was marketed under this system is surgical mesh which under the grandfathering programme was classified as medium risk even though it is implanted surgically and intended to remain in place over the patient's lifetime. In essence, grandfathered devices permitted placement of thousands of devices onto the market without any regulatory oversight by the FDA.

After the Medical Device Amendments of 1976, high risk devices could gain market access via two regulatory pathways, the 510(k) route or PMA (pre-market approval).

The PMA process entails submission of robust scientific evidence and clinical trial data to support safety and effectiveness of the device.

Under the 510(k) route manufacturers could claim the device is significantly equivalent to an existing marketed device known as a predicate device. The PMA process is both time consuming and expensive, so the 510(k) route offers manufacturers the opportunity to demonstrate equivalence to another device without conducting a clinical trial. Again, this system is flawed and allowed for grandfathered devices to be used as predicate devices. Additionally, a predicate device used for the purpose of demonstration of significant equivalence may have been withdrawn from the market for safety reasons.

A review of the regulatory ancestry network of surgical meshes by Zargar and Carr (2018) highlights the flawed nature of the US 510(k) pathway and the resulting impact on patient safety. As previously mentioned, surgical mesh scandals have been widely broadcasted. Many surgical meshes entered the US market via the 510(k) pathway. The 510(k) pathway allows for previously cleared meshes to act as predicate devices for newer products. Zargar and Carr traced the ancestry of surgical meshes cleared using the 510(k) route to determine their linkage to devices that have been recalled for patient safety reasons. The study concluded that of 77 mesh devices 510(k) cleared within a 3-year period were based on equivalence to 400 devices. Furthermore, 97% of the devices were linked to six products that were placed on the market before 1976. Prior to 1976, regulation of devices was limited to prohibition of adulterated or misbranded product, there was no requirement at that time to demonstrate the safety and efficacy of the product. A total of 16% of devices that received FDA clearance within the mentioned 3-year period were descended from 3 devices that had been recalled for patient safety reasons. Although there is a legal obligation to present scientific evidence to support the claim of substantial equivalence, the original device may have limited or insufficient data. This demonstrates that undetected design flaws and quality issues may passed down through generations of devices using this regulatory pathway. These findings show that the 510(k) route is not always sufficient to protect patients.

The resultant patient safety issues lead to numerous lawsuits prompting reclassification of some meshes for treatment of Pelvic Organ Prolapse repair from Class II to Class III where a PMA is required.

2.4 BENEFITS OF THE NEW EU REGULATION MDR 2017/745

The main goal of MDR 2017/745 is to enhance user safety and ensure devices placed on market are safe and effective. The previous Directives were ill-equipped to govern the technological advancements that have been seen in devices in recent years.

Requirements for compliance to the MDR are established in Annex 1, General Safety and Performance Requirements. Compliance to the GSPRs is demonstrated through use of harmonized standards as published in the Official Journal of the European Union or use of Common Specifications (CS). Through manufacturers application of standards and CSs, patient safety is enhanced by ensuring adherence to state-of-the-art processes. Manufacturers must also select the appropriate conformity assessment route for their devices based on the use of the device and level of risk associated with the device.

Four classes of medical device are described in MDR (I, IIa, IIb, and III). The level of control and monitoring of the manufacturer is also dependent on the risk class of the device. For self-declared devices, there is no involvement by a Notified Body or a Competent Authority. All other devices have varying degrees of Notified Body involvement and/or CA involvement. This third-party oversight of medical devices improves patient safeguarding.

Class I Devices

Self-certified devices are required to hold a technical file in accordance with Annex II and III. There are additional requirements for devices supplied sterile, that have a measuring function or are reusable surgical implements. For these devices a QMS must be established, and production controls put in place. Notified Bodies will also play a role in monitoring the QMS.

Class IIa Devices

Class IIa devices must undergo conformity assessment and have in place a full QMS according to Annex IX. The manufacturer has the option to also prepare technical documentation in accordance with Annex II and III and demonstrate production controls according to Annex IX.

Class IIb Devices

Class IIb devices are broken down into different groups:

- Implantable devices
- Active devices that administer or remove a drug product
- Any device not covered by the 2 groups above

Control of Class IIb devices is closely aligned with that of Class III devices. In contrast to Class III devices there is generally no expert panel review required for Class IIb products nor is there a separate CE certificate issued for the technical documentation file. An expert panel review is required in the case of active devices intended to administer or remove medicinal substances. Technical documentation review for Class IIb products is based on a sample of device type unless the product is implantable, these devices require 100% review by the Notified Body.

Class III Devices

Class III devices are the highest risk and therefore have the strictest controls. A full technical documentation review is required along with a Quality Assurance audit. An expert panel review is also required for implantable devices. This review enhances patient safety.

The classification rules cover more product and technology groups than the previous Directives and, in many instances, products have reclassified and been raised to higher risk categories under MDR.

2.5 AREAS FOR IMPROVEMENT IN EU

CLINICAL TRIALS

An area of improvement within the EU is Clinical trials; in particular, study design and patient numbers. For medicinal product clinical trials, it is well known that blinded RCTs are the preferred approach. A blinded study presents a massive challenge with medical devices as for many implantable devices this is near impossible, a placebo may also be unethical and expose a patient to unnecessary risk. There is also a strong placebo effect for devices such as an intra-articular sodium hyaluronate device as a patient may be prone to greater placebo effect than with a medicinal product. The data from a clinical trial for this type of product is also greatly influenced by the administration technique, poor technique may result in discomfort for the patient and in the case of injection into the wrong area may result in pain and infection.

Presently the medical device industry must rely on Good Clinical Practice. ICH GCP Guideline for good clinical practice E6(R2) is a globally recognized started for management of clinical trials for human subjects.

Table 8 – GUIDING PRINCIPLES FOR CLINICAL TRIALS

1	Trials should be conducted with ethical principles rooted in the Declaration of Helsinki and in accordance with GCP and regulatory requirements.
2	Prior to initiation of a trial the benefit/risk must be determined, a trial should not proceed unless the benefits outweigh or justify the risks.
3	The rights and safety of the subjects is of most importance.
4	Available data should support the proposal for a clinical trial.
5	A detailed protocol using scientifically sound methods is required.
6	The trial must be conducted in accordance with the protocol. The protocol must be approved by IRB (Institution Review Board) or IEC (Independent Ethics Committee).
7	Subjects should always be under supervision of qualified physicians.
8	All personnel involved must be trained and competent to perform their task(s).
9	All subjects must give their Informed Consent freely prior to the trial.
10	Clinical trial data must be recorded and documented in a reliable manner to allow accurate reporting and interpretation.

11	Identity of subjects must be protected in accordance with regulatory requirements.
12	Investigational products must be manufactured and handled in accordance with GMP.
13	Any systems used must be adequate to ensure reliability of the data.

For medical devices in the EU, ISO 14155 highlights the principles that should be followed in order to comply with GCP (Good Clinical Practice).
Topics covered by this standard include the following:

- Ethical Considerations
- Responsibility of Sponsor and Investigators
- Planning and Conducting Clinical Investigations
- Close Out of a Clinical Investigation

Ethical Considerations
All participants must be informed of the purpose and nature of the study. Participants must clearly understand all risks and benefits involved. ISO 14155 prohibits use of vulnerable populations such as the elderly or children unless the investigation is impossible without inclusion of these subjects. To guarantee investigations are conducted in accordance with GCP, independent oversight is required to safeguard subjects.

Responsibilities of the Sponsor and Investigator
Clause 8 of ISO 14155 lays out the responsibilities of the Sponsor and Clause 9 lays out the responsibilities of the Investigator.
The Sponsor must plan and carry out the investigation in a way that complies with quality assurance and quality control requirements. The sponsor may use a qualified contractor to conduct the investigation but retains full responsibility for the activity.
The Investigator (Principal Investigator) is responsible to management of the investigation in accordance with the Clinical Investigation Plan (CIP). Ensuring the integrity of data collected and safeguarding of subjects are key roles within the Investigators remit.

Clinical investigation planning and conduct
Prior to initiating a clinical investigation, a detailed CIP must be reviewed and approved by the ethics committee and relevant regulatory agency.
The CIP details the research objectives, study design, study methodology and methods of analysis. No changes can be made to the CIP without prior approval by the ethics committee and involved regulatory agency.
ISO 14155 stipulates that all risks related to the investigation must be considered. It is imperative that the risks posed are understood in relation to the benefits to the subjects and also society.
All participants in the study must be protected and data safeguarded.

Closing out a clinical investigation
Clause 7 of ISO 14155 describes how to close out a clinical investigation. Clause 7 also provides guidance in the event of early termination or suspension of an investigation. Preparation of the clinical investigation report is also described in this Clause and the requirements for retention of investigation documents are also described.

SUMMARY

This section presents the literature review considered as secondary research. The findings of the literature review are summarized as follows:

- Osteoarthritis is a degenerative disease impacting QoL of patients.
- IAHA medical devices are used commonly in OA Management.
- There is a lack of clinical data for both IAHA and PRP products available.
- New MDR requirements and classifications will enhance patient safety.
- MDR requirements may lead to a reduction of medical devices available on the EU market as manufacturers struggle to meet the requirements.
- MDR does not allow for “grandfathering in” in comparison to the US framework.
- Guidance documents issued by MDCG on Clinical Evidence are well written but they do not answer the fundamental question for legacy device manufacturers – how can we gather sufficient clinical evidence.

Key documents reviewed are included in the table presented below.

2.6 REGULATORY TEXTS

Year	Author	Title	Aims & Methodology	Conclusions
2019	Medical Device Co-Ordination Group	MDCG 2019-14 Explanatory note on MDR codes	This guidance document explains the MDA/MDN, MDT and MDS codes applicable under MDR.	This document is key for appropriate categorisation of devices under MDR. These codes group products by technology, intended purpose, manufacturing methods etc., This document is included as it explains the coding system under MDR.
2020	Medical Device Co-Ordination Group	MDCG 2020-5 Clinical Evaluation – Equivalence - A guide for manufacturers and notified bodies April 2020	This guidance document aims to explain demonstration of equivalence to an existing on-market product for the purpose of obtaining CE certification under MDR. The document achieves this by analyzing differences between MEDDEV 2.7/1 rev.4 and MDR requirements.	This document included as it is key for understanding the MDR requirements related to claiming equivalence to other on market products. The document explains equivalence in terms of technical characteristics, Biological characteristics and Clinical characteristics. Manufacturers must present scientific justification for any differences in characteristics when claiming there are no significant differences Scientific justifications shall be provided for the different characteristics when claiming no clinical difference in safety and performance.

2020	Medical Device Co-Ordination Group	MDCG 2020-6 Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC A guide for manufacturers and notified bodies April 2020	This document aims to provide guidance for Notified Bodies and manufacturers on providing clinical evidence to fulfil the requirements of the relevant General Safety and Performance Characteristics of the MDR. This document aims to provide guidance for manufacturers and notified bodies to prepare for the conformity assessment procedure according to the MDR. The guidance document discusses Articles 6.1 – 6.5 of MDR Annex XIV Part A Section 1 and provides an explanation of the requirements.	The document is included as it provides a framework for manufacturers to prepare a clinical evaluation. Although the document highlights the GSPRs and clinical data required it is limited as it does not provide guidance on the methodology that should be used to collect sufficient clinical evidence. It is also limited as it does not provide guidance for different classes of device or technology groups. The guidance document provides a framework for Notified Bodies and manufacturers to prepare a clinical evaluation.

2021	Medical Device Co-Ordination Group	MDCG 2021-25 Regulation (EU) 2017/745 - application of MDR requirements to 'legacy devices' and to devices placed on the market prior to 26 May 2021 in accordance with Directives 90/385/EEC or 93/42/EEC October 2021	This document aims to provide guidance on MDR requirements that apply to legacy devices placed on the market under the directives. MDCG analyses the requirements laid out in Chapter VII of the MDR and their applicability to legacy devices.	This guidance document is selected as it is specifically written as a guide for legacy device manufacturers. This document concludes that MDR requirements pertinent to PMS, Vigilance, Market Surveillance, Economic Operators and PSUR apply for legacy device manufacturers.
2021	Medical Device Co-Ordination Group	MDCG 2021-6 Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation April 2021	This document is intended to answer questions of sponsors of clinical investigations carried out for the purpose of CE marking under MDR.	The document highlights the process for conducting a clinical investigation but does not provide a methodology that should be used to collect sufficient clinical evidence. The document serves to define the differences between MDR and the previous directives, explain terms such as clinical evidence, clinical performance, clinical benefit and outlines the process for conducting a clinical investigation.

2021	Smirthwaite. A	Clinical evaluation under EU MDR	This white paper provides and overview of how requirements for clinical evaluation of medical devices have evolved over time. This paper analyses the requirements defined in Article 61(1) of the EU MDR to define the process of clinical evaluation.	This white paper is focused on the purpose of clinical evaluation and describes the process of clinical evaluation. This paper is included as it describes the clinical evaluation process but is limited as it does not describe a methodology for gathering sufficient clinical evidence.

2.7 ACADEMIC ARTICLES & STUDIES

Year	Author	Title	Aims & Methodology	Conclusions
2015	Kawano MM, Araújo IL, Castro MC, Matos MA	Assessment of quality of life in patients with knee osteoarthritis	The purpose of this study is to the determine the Quality of Life of Knee OA patients. The study is a cross sectional study of 93 patients.	The study concludes that patients with OA have a low perception of their quality of life in terms of pain, functional capacity and functional limitations. This study is included as it highlights the issues encountered by OA patients.

2016	Migliore, A, Bizzi, E, De Lucia, O, Delle Sedie, A, Bentivegna ,M, Mahmoud, A, Foti, C	Differences among Branded Hyaluronic Acids in Italy, Part 1: Data from *In Vitro* and Animal Studies and Instructions for Use	The aim of this study is to identify scientific evidence from studies conducted on intra-articular hyaluronic acid products available on the Italian market. This study also reviews the IFUs of the available products to determine the accuracy of information given considering the scientific evidence available.	The study concludes that these on market devices are lacking in scientific evidence and recommends brand-specific studies are conducted to aid clinician decision making. This study is valuable as it indicates that the existing products, which are legacy devices are lacking in clinical evidence. The recommendation for brand-specific studies to aid clinician decision making raises a question around clinician understanding and confidence in these products that will be incorporated into the primary data collection for this dissertation.
2017	Dermot J. Bowden, Caoimhe A. Burke, Abdullah Alkhayat, Stephen J. Eustace, Eoin C. Kavanagh	Injectable Viscoelastic Supplements: A Review for Radiologists	This study reviews efficacy of IA HA for OA in treatment of joints other than the knee.	The article conclude that chemically cross-linked HA tends to result in more adverse events than non–cross-linked HA. The article states that although the evidence available is limited to support efficacy, IAHA treatment remains in common use.

2018	Clemens, N	The European Medical Device Regulation 2017/745/EU: Changes and Impact on Stakeholders	This journal reviews the main changes introduced by the MDR relevant for Economic Operators and Notified Bodies.	This journal is included as it details a comprehensive list of new requirements for both Notified Bodies and Economic Operators. It concludes that both Economic Operators and Notified Bodies have a significant task to undertake in order to meet the requirements of the regulation.
2020	Billesberger, L, Fisher,K. Qadri,Y, Boortz-Marx, R	Procedural Treatments for Knee Osteoarthritis: A Review of Current Injectable Therapies	This study determines the prevalence of knee OA in the Canadian region and discusses current available treatment options for patients. The study reviews current available treatments and their categorization according to various expert groups in the OA field.	The study concludes that although PRP (platelet rich plasma) therapy is beginning to replace HA injections and corticosteroids, larger trials are required to confirm the safety and efficacy of this treatment.
2020	Behan, R, Watson, M, Pandit, A	New EU medical device regulations: Impact on the MedTech sector	This article aims to compare the MDR to the previous Directives and discusses the impact in the Irish MedTech industry**.** The information sourced by CÚRAM is gathered from the Irish MedTech sector.	The article concludes that the introduction of the MDR brings challenges for manufacturers in terms of gathering clinical evidence, supply chains, Quality Management System upgrades. The article also highlights that these changes may be costly and labour intensive. The article is included as it succinctly distinguishes between the requirements of the directives and the MDR. The article is

				limited as it is focused on innovative products rather than legacy products.
2020	Maresova, P, Hajek,L, Krejcar, O, Storek, M, Kuca, K	New Regulations on Medical Devices in Europe: Are They an Opportunity for Growth?	This study seeks to examine the medical device industry in the Czech Republic versus other global markets in relation to medical device innovation and MDR. It closely examines barriers to innovation that come with regulation. The study aims to review production issues associated with compliance requirements particularly for innovative products. The study is based on statistical surveys from international organizations such as OECD and WHO	The study concludes that regulation in the EU has led to reduced patent activity in the Czech Republic. In contrast, there has been no decline in patent activity in the US. This information is valuable as it points to EU regulation being a barrier to innovation, this is not necessarily the case in the US. The struggles faced by legacy device manufacturers seems to be comparable to that of innovative firms.
2020	Rosen, J, Niazi, F, Dysart, S	Cost-Effectiveness of Treating Early to Moderate Stage Knee Osteoarthritis with Intra-	The study reviews the cost effective-ness of treating knee OA sufferers with High Molecular Weight HA versus Low Molecular Weight HA stage of OA. This study employs analytic models to determine responsive rate to	This study concludes the High Molecular Weight combined with physical therapy is a cost-effective treatment option for patients suffering with mild to moderate OA.

		articular Hyaluronic Acid Compared to Conservative Interventions	treatments at varying stages of the disease. The models compare treatment response rates against the cost per quality adjusted life year.	
2021	Pavone,V, Vescio,A, Turchetta,M, Chiara Giardina,S. Culmone, A, Testa, G	Injection-Based Management of Osteoarthritis of the Knee: A Systematic Review of Guidelines	This study aims to collect international guidelines to provide a comprehensive overview of injectable treatments for knee OA.	The study concludes that the effectiveness of corticosteroids is short-lived but High Molecular Weight HA injections provides a positive outcome for patients over a course of injections. This study is included as it strengthens the stance that intra-articular injections of hyaluronic acid are an effective treatment for knee OA.
2023	Kearney, B, McDermott, O	The Challenges for Manufacturers of the Increased Clinical Evaluation in the European Medical Device Regulations: A Quantitative Study	The aim of this study is to determine the impact of increased clinical evaluation requirements on medical devices manufacturers. This study uses a quantitative survey gathering responses for 68 individuals working in the medical device industry in either QA or RA roles.	The study concludes that the main source of reactive PMS data collected by manufacturers is complaints and the main source or proactive data is from PMCF. The investigation concludes that the greatest challenge to manufacturers is understanding the volume of data needed to generate sufficient clinical evidence and also a lack of transparency in Notified Body expectations. The report highlights the challenges for manufacturers and the potential for market shortage.

2023	Dermot J. Bowden, Stephen J. Eustace, Eoin C. Kavanagh	The value of injectable viscoelastic supplements for joints	The aim of this article is to review the mechanism of action of IA HA devices, review practice of administration (including associated guidelines) and also adverse events associated with these devices.	Clinical evidence is sparse regarding efficacy of viscosupplementation and the writers do not use this treatment as first line treatment. It is recognized in this article that the products have value in patients who are not eligible for NSAIDS or corticosteroids. The authors recommend viscosupplementation only after other treatments such as physical therapy, basic pharmacological treatment, and first-line joint injection with corticosteroid have not given adequate relief to the patient.

CHAPTER 3: RESEARCH METHODOLOGY

This research study aimed to investigate the following:

1. To examine key MDR 2017/ 745 compliance challenges for legacy devices, in particular, the impact of MDR clinical evidence requirements.

2. To compare current EU MDR 2017/745 framework versus US medical device regulatory framework and pharmaceutical product requirements with respect to clinical data.

3. To discover potential impact on patients in the event of market shortage for implantable, intra-articular medical devices.

4. To propose possible routes forward for industry and regulators to ensure continuity of supply of implantable, intra-articular medical devices.

3.1 RESEARCH METHOD USED

This section aims to explain the research process of defining the research problem. This section discusses the research philosophy, research approach, research strategy, methods chosen, time horizons and technique using the research onion described by Saunders *et al.* (2007) as a guide.

According to Saunders et al (2007), there are six layers to the research onion and each layer needs to be peeled away to come to the center point which is the data collection and analysis.

At the outset of this project, selection of the area of focus was of critical importance. The initial focus was on selecting an area of interest and the research questions were established following review of available literature. An in-depth literature review was carried out to develop a hypothesis of key problems for manufacturers posed by MDR 2017/745.

Identification of the main changes introduced by MDR allowed me to consider the main areas for examination through the primary research. The key problems for manufacturers may result in lack or delay in certification, this gives rise to a patient problem in the event of a market shortage. A critical examination of key literature allowed for definition and refinement of the core questions. Other items considered were time constraints, availability and access for information and the ethics.

The research questions were defined as follows:

Question 1. What are the key MDR 2017/ 745 compliance challenges for legacy devices, in particular, the impact of MDR clinical evidence requirements.

Question 2. What are the differences between current EU MDR 2017/745 framework and US medical device regulatory framework and pharmaceutical product requirements with respect to clinical data.

Question 3. What is the potential impact on patients in the event of market shortage for implantable, intra-articular medical devices.

Question 4. What routes are possible for industry and regulators to ensure continuity of supply of implantable, intra-articular medical devices.

The questions for the interviews and questionnaire were established from the secondary research. The goal of the questionnaire was to determine if my understanding of the key compliance challenges is

aligned with the opinions of other professionals within the industry. The questionnaire is also aimed at reinforcing the findings of the secondary research. In my opinion, the challenges of MDR present a potential risk to supply of product and as result a patient impact, I would like to confirm this hypothesis.

This potential for patient impact led me to the interviews targeted at patient interfacing experts.

I believe that this approach allows for gathering a well-balanced view of the MDR impact for both industry and patients with respect to legacy intra-articular medical devices.

3.2 RESEARCH PHILOSOPHY

Research Philosophy is the way in which the researcher views the world. As a Regulatory Affairs professional in the medical device industry the difficulties encountered by manufacturers as they navigate the MDR is an area of interest for me and an area I am actively involved in.

There are three areas for consideration in terms of research philosophy: epistemology, ontology and axiology. Epistemology is concerned with what is accepted as valid knowledge. Ontology is concerned with the assumptions we make about reality. Axiology is concerned with our value systems.

My theoretical perspective is the basis of the philosophy used to develop the research strategy. The theoretical perspective is interpretivist in nature as it requires opinions in order to make sense of issues encountered by both manufacturers and patients as a result of the MDR.

In terms of data collection related to this topic, accessibility to the opinions of professionals within the medical device and clinical field are key to collection.

3.3 RESEARCH APPROACH

According to Saunders et al (2007), research approach can be defined as deductive and inductive. The deductive research approach involves developing a theory and a hypothesis and then testing the hypothesis. Deductive research is generally linked to quantitative data. The inductive research approach involves collecting data and developing a theory based on the data collected. Inductive research is generally linked to qualitative data. The intent of this study is to determine the challenges faced by manufacturers, potential patient problems and also propose solutions for industry and regulators.

As this research is based on surveys and interviews it is both deductive and inductive in nature.

3.4 RESEARCH STRATEGY

Both qualitative and quantitative strategies have been selected for this research. The theories will be based on the opinions of study participants. This is Grounded theory where the researcher forms the theory based on the views of the subjects.

Other strategies such as ethnography or phenomenological research are not relevant for this study as the challenges faced by manufacturers and patients can only be determined by accessing views and opinions of professionals within the medical device and clinical fields. Understanding the challenges and opinions of these groups will allow for proposals for improvement.

3.5 RESEARCH CHOICES

According to Saunders *et al.* (2007), a researcher can use a Mono method which is a single method of data collection or a Multi method which is use of more than one method of data collection. This research uses a Multi method in the form of a Questionnaire and Interviews. The questionnaire is structured and uses a likert scale or multiple-choice option to gather data. The questionnaire is broken into themes to allow for flow of questions and ease of interpretation. The interviews are based on themed, structured and open-ended questions to gain further insight into the views of the participants. The use of interviews adds further validity to the research as it seeks to understand the true value of the studied devices and the knock-on effect for patients in the event of market shortage. This patient impact is at the core of the research as the primary goal of the MDR is to enhance patient safety. Patient safety is crucial but what if the regulatory requirements are too stringent to allow for commercialization of products that significantly improve a patients Quality of Life?

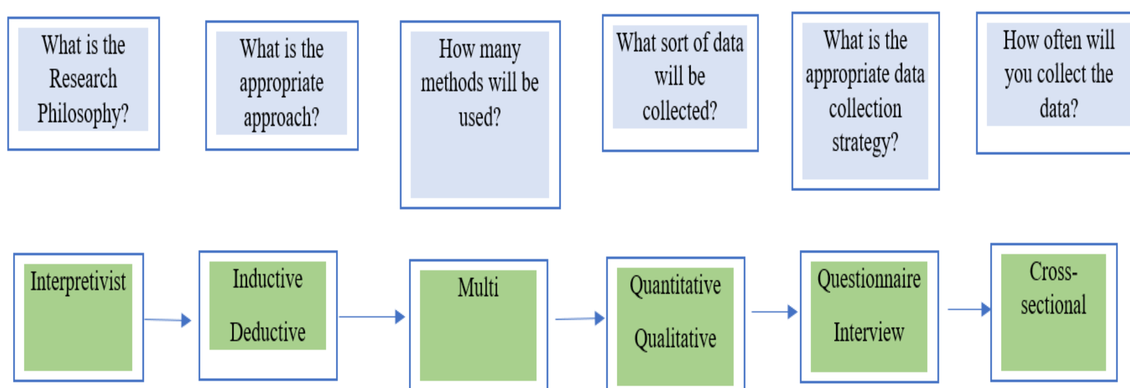
3.6 TIME HORIZONS

This study is a cross-sectional study as is captures a snapshot of the opinions of experts at a given point in time. Three months was allocated for collection of data.

3.7 TECHNIQUES & PROCEDURES

As mentioned, data from questionnaires and interviews will be collected and analysed. The questionnaire is aimed at professionals within the medical device industry to understand the difficulties faced and the interviews with Clinical, Pharmacy and Sales & Marketing experts seeks to understand the value of intra-articular medical devices and knock-on effect for patients in the event they cannot access these products.

The Research Methodology can be summarised as follows:



3.8 ETHICS CONSIDERATIONS

In accordance with Economic and Social Research Council, (ESRC) UK – Guidelines, the following points will be of paramount importance:

- Research shall be collected and reviewed in a manner that ensures quality and integrity.
- All participants will be fully informed of the scope, purpose, recording and compilation of findings.
- All participants will be fully informed of the level of participation needed from them.
- All information provided by participants shall be confidential and anonymous.
- Participants are involved voluntarily.
- Harm to participants shall be avoided.
- The research must be independent and free from conflicts of interest.

The completed Ethics Application form was submitted prior to beginning the study and is attached as an appendix (Appendix 2).

3.9 QUESTIONNAIRE/SURVEY

A questionnaire has been used to gather data from experts working in the medical device industry. A questionnaire has been selected as it allows for collection of information using multiple choice options to gauge industry expert opinion. The questionnaire was presented as a Microsoft Teams Form as it is a professional presentation which allows data to be exported with ease. I chose the questions based on the secondary research and my own experiences within the medical device industry.

For this research the preference was to gather data from those who have been working in the industry for several years and have therefore had exposure to MDD and MDR requirements. Information was predominantly gathered for legacy products, but innovative products were also considered.

The structure of the question was based on themes. Themes were divided into General Questions (Demographic Information), General Questions related to MDR 2017/745, Clinical Evidence Questions and Outsourcing of Activities/ Business Impacts.

Many of the questions are presented using a likert scale. Collection of information in this manner was chosen as this approach provides the following advantages:

- Easy for the respondent to understand.
- Provides more meaningful data than simple yes and no answers.

The likert scale is limited in that the respondent cannot explain the reason why they feel a certain way with respect to a given topic. The benefit of supplementing the questionnaire with interviews gives a greater insight into the patient experience which is of paramount importance when trying to understand the 'big picture' patient impact of the new Medical Device Regulation.

A copy of the Questionnaire is attached as Appendix 3.

3.10 INTERVIEW

Interviews involved one-on-one discussions between the researcher and the interviewee. Interviewees were selected on the basis of their knowledge in the Clinical or Sales and Marketing field. The interviewees are also experts within the Orthopedics fields, many of the interviewees are Orthopedic surgeons or experts. These expert opinions are crucial for understanding the value of these products in terms of patient QoL, benefits/ risks of alternative treatments and the impact potential market shortages could bring. An interview was selected as it allows participants to provide detailed answers to questions so that I may understand their responses fully. In a similar manner to the questionnaire, the questions were developed using a themed approach. The themes are divided into General Questions (Demographic Information), General Questions relating to Osteoarthritis, Specific Questions relating to Intra-articular medical devices and Questions related to patient impact in the event of a market shortage. The interview is designed as open-ended questions to allow for flow of conversation and ease of information gathering.

A copy of the Interview is attached as Appendix 6. Prior to conducting the interviews, participants were given a Participant Information Letter (Appendix 5) and requested to complete an Informed Consent Form (Appendix 4).

CHAPTER 4: FINDINGS AND DISCUSSION

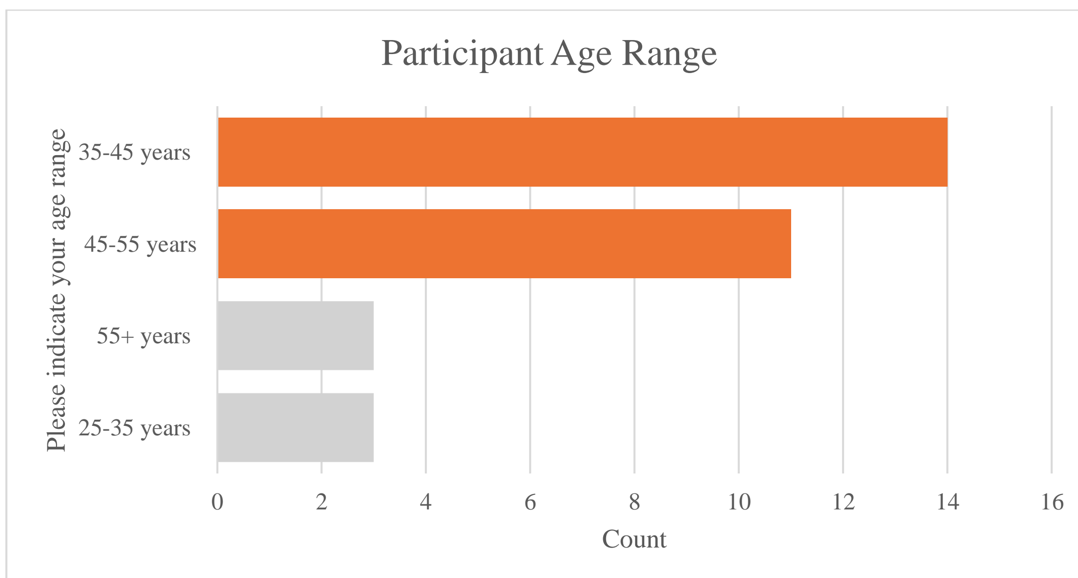
4.1 INTRODUCTION

In this chapter the findings from primary data collection are discussed and analysed. Primary data was collected in two forms, a questionnaire aimed and professionals within the medical device sector with experience in the challenges presented by MDR 2017/745 and through interviews with Clinical and Sales and Marketing experts to fully assess the value of the products in terms of patient QoL and the patient impact in the event of a market shortage. Data is presented in tabular and graphical form to ensure ease of interpretation of the data.

4.2 QUESTIONNAIRE

4.2.1 DEMOGRAPHIC INFORMATION

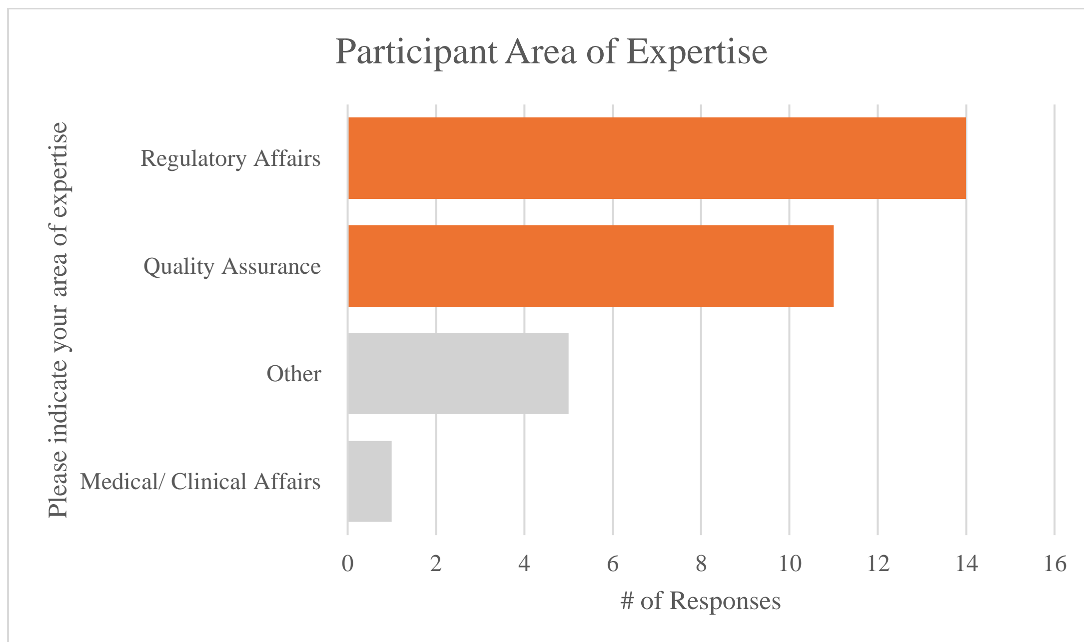
Participant Age Range



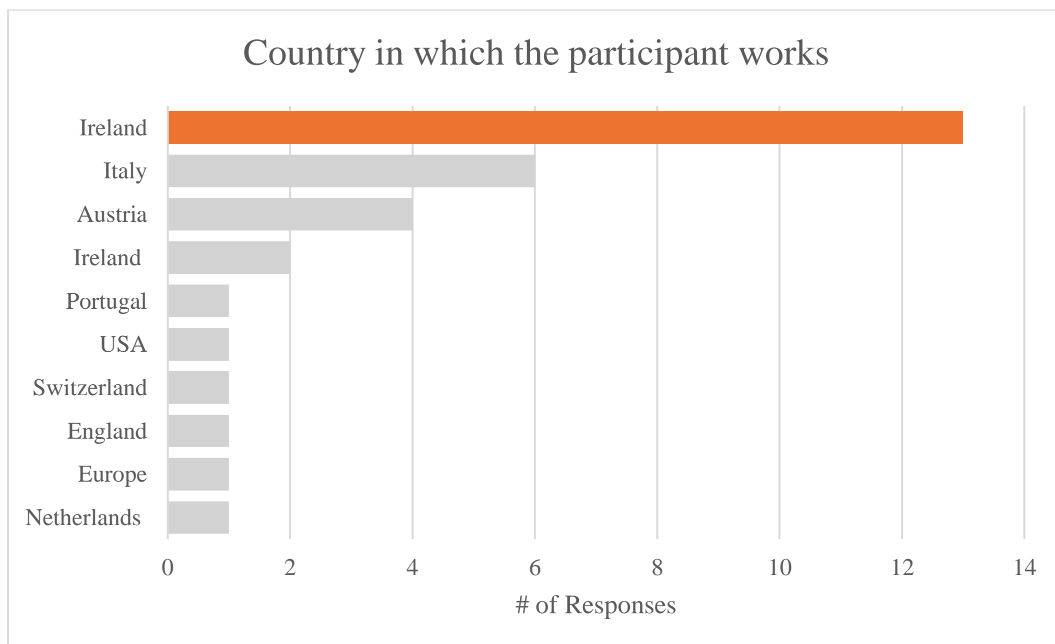
Years of experience in the Medical Device Industry

Years of experience in the medical device field	# of Responses
15 - 20 years	8
10 - 15 years	7
5 - 10 years	6
0 - 5 years	6
20+ years	4
Grand Total	**31**

Participant Area of Expertise



Country in which the participant works

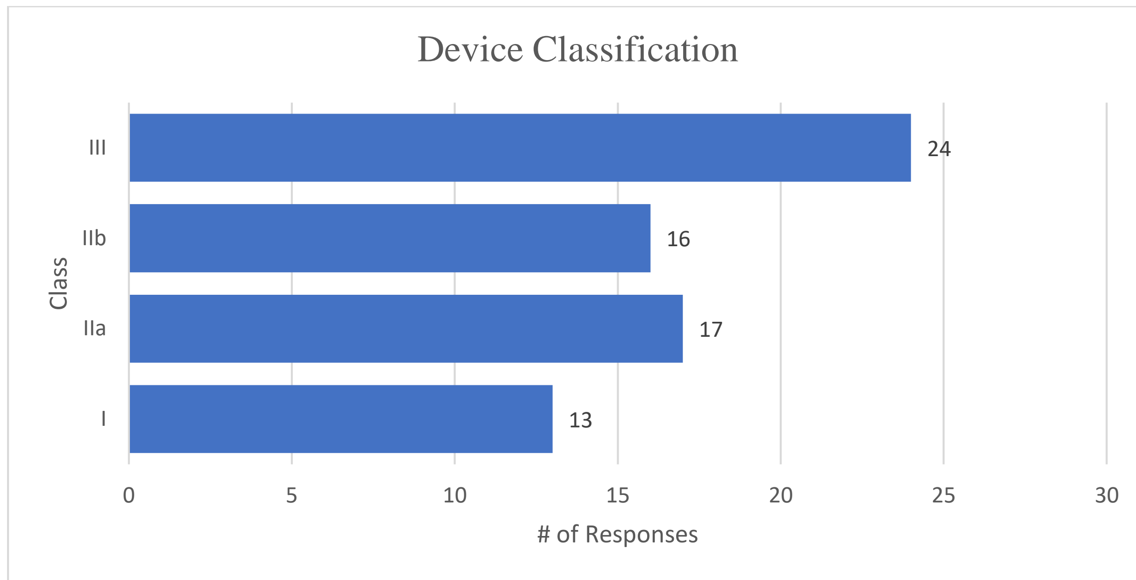


Commentary

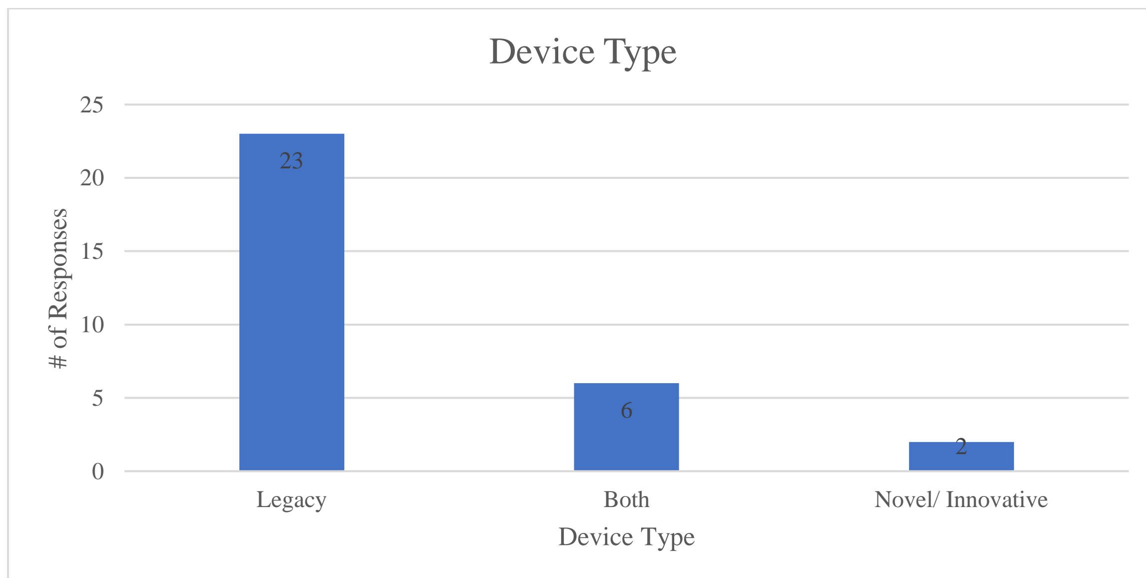
The data shows that the participants are predominantly over the age of 35 years, are predominantly Regulatory Affairs or Quality Assurance experts with greater than 5 years' experience. Additionally, most participants are working within the EU. The demographic information indicates that the participants are mature, experienced, and well informed of EU MDR 2017/745 requirements. The age and experience profiles also indicate the participants have knowledge and have worked under the MDD framework also so are well suited to respond to questions regarding MDR impact.

4.2.2 GENERAL QUESTIONS RELATED TO MDR

Question - Please indicate the classification of your medical devices under MDR 2017/745



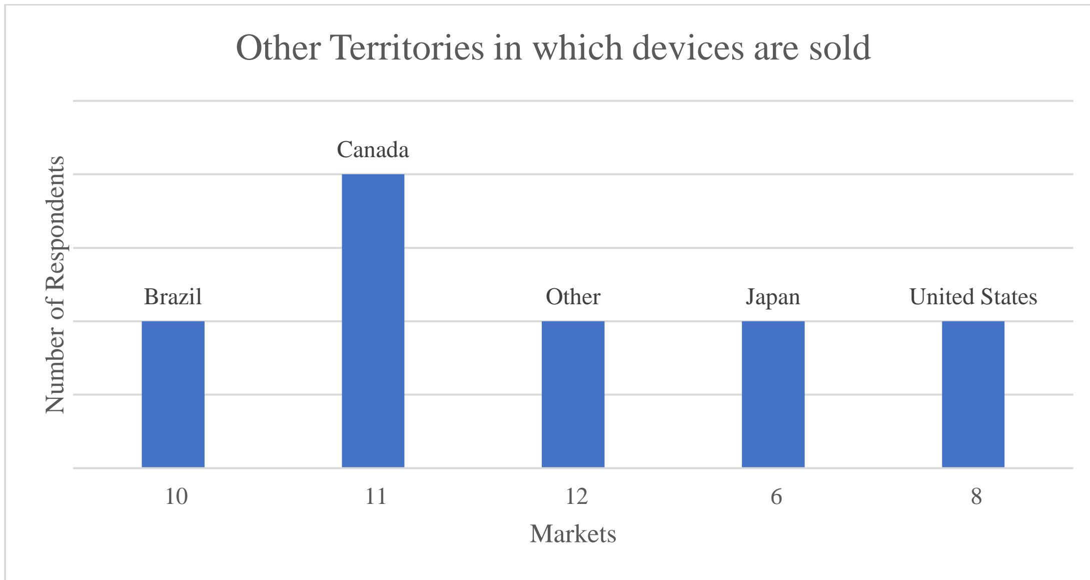
Question – Please indicate Device Type



Question - Please indicate if your device has been reclassified according to MDR 2017/745

Please indicate if your device has been reclassified according to MDR 2017/745	# of Responses
Yes	17
No	14
Grand Total	**31**

Question - Please indicate other territories in which your devices are sold



Question - To what extent do you agree with the following:

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Notified Body scrutiny procedure for higher risk devices is clear to me	1	2	13	13	2
Requirements related to registration of Economic Operators are clear to me	1	1	6	18	2
I understand EUDAMED functionality and registration requirements	1	4	7	14	5
Increased scrutiny of the supply chain has been a challenge for my organisation	1	3	7	17	3
MDR 2017/745 Technical Documentation requirements are clear to me	1	3	9	15	3
Unique device identifier requirements are clear for each device class	2	9	5	12	3
Labelling Requirements & relevant GSPRs are clear for me	1	4	4	19	3

Post Market Surveillance requirements are clear for me	1	1	4	15	3
Vigilance Reporting Requirements are clear for me	1	1	10	13	6

Question - To what extent do you agree with the following:

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Preparation of Technical Documentation according to MD 2017/745 has been costly for my organisation	0	1	1	17	12
Preparation of Technical Documentation according to MD 2017/745 has been labour intensive for my organisation	0	0	1	13	17
Additional resources have been employed by my organisation to meet MDR 2017/745 requirements	0	2	4	13	12
There is sufficient support available from regulatory bodies to provide guidance for manufacturers to meet MDR 2017/745 requirements (Notified Bodies and Health Authorities)	3	7	13	8	0
The transition period for compliance with MDR 2017/745 is sufficient	1	3	9	17	1

Commentary

The respondents work primarily with higher risk, legacy devices some of which have been reclassified under MDR 2017/745. More participants indicate their devices have been reclassified than expected (17/31). Information regarding high-risk legacy devices is of most value for this study as the topic is centered on legacy, high risk devices. The respondents also have experience in markets outside of the EU, which gives further value to their responses as they understand regulatory structures outside of the EU and how the EU system compares with others.

From the data, respondents mainly agreed they understand requirements related to the MDR requirements such as Notified Body Scrutiny procedures, Economic Operator registration, EUDAMED, Technical documentation, Vigilance, PMS, UDI, Labelling and GSPRs. 20/31 respondents indicate that Supply Chain scrutiny has been a challenge for their organization. This is an

area not predicted by the researcher. The difficulties related to Supply Chain scrutiny is a topic that could be explored as a separate study.

In terms of the research objectives key compliance challenges are clear with respect to Technical Documentation preparation, with the vast majority agreeing that this has been challenging from both cost and labour perspectives. The data also shows 25 respondents report an increase in personnel needed for their organisation.

Although respondents agree that there is sufficient time allowed for transition to MDR the responses indicate that there is not sufficient support from regulatory agencies in terms of guidance provided, only 8 responses were positive in this regard.

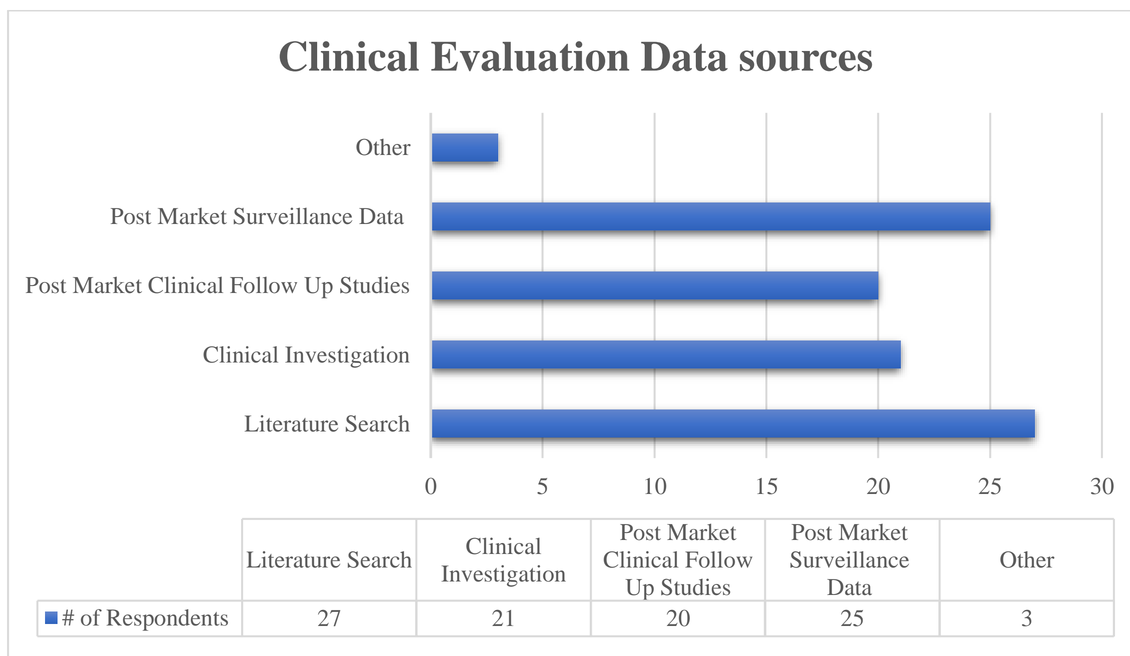
This is aligned with the hypothesis of the researcher, the transition period is sufficient but there is a lack of support from regulatory agencies for specific groups of devices.

4.2.3 CLINICAL EVIDENCE QUESTIONS

Question - Under MDD 93/42/EEC, did your organisation claim equivalence to another device in order to meet clinical evidence requirements.

Under MDD 93/42/EEC, did your organisation claim equivalence to another device in order to meet clinical evidence requirements.	**No**	**Yes**	**Grand Total**
# of Responses	**8**	**23**	**31**

Question - Please indicate the sources of Clinical Evaluation Data used by your organization to comply with MDR 2017/745.



	Literature Search	Clinical Investigation	Post Market Clinical Follow Up Studies	Post Market Surveillance Data	Other
# of Respondents	27	21	20	25	3

Question - With respect to Clinical Evidence required for your device(s) please indicate Yes or No for the following statements:

	Yes	No	N/A
Guidance documents MDCG 2020-5 & MDCG 2020-6 provide adequate guidance on clinical evaluation requirements from MedDev 2.7/1 rev 4 and Article 61 and Annex XIV Part A of the EU MDR	21	5	5
I understand methodologies that should be used to collect sufficient clinical evidence for my device(s)	21	7	3
Clinical evidence gathered for my devices under MDD 93/42/EEC is sufficient to support the intended purpose and associated clinical benefits of the device(s) as well as the conditions of use and specific contraindications	12	17	2
Clinical evidence gathered for my devices under MDD 93/42/EEC is sufficient to support all indications statements	12	17	2
Clinical evidence gathered for my devices under MDD 93/42/EEC is sufficient for all potential patient populations	16	13	2
Clinical evidence gathered for my devices under MDD 93/42/EEC is sufficient to support all device variants and combinations	13	12	6
Clinical evidence gathered for my devices under MDD 93/42/EEC is sufficient to support the device lifetime in use	16	12	3

Question - In order to comply with MDR 2017/745 requirements regarding clinical evidence has your organisation revised the following –

	Yes	No
Device Intended Purpose	17	14
Device Indications	22	9
Device Contraindications	20	11
Residual Risks associated with use of the device	22	9

Question - If yes selected for any item listed in question above please indicate if the changes are expected to have a negative patient impact i.e., is it likely that there will be a restriction in patients accessing the device.

Answer	Number of Responses
N/A	4
No	18
Yes	9
Grand Total	**31**

Question - If yes selected for any item listed in question above please indicate if the changes are expected to impact registrations in markets outside the European market.

Answer	Number of Responses
N/A	5
No	14
Yes	11
Grand Total	**30**

Note - 1 response was blank for this question.

Question - If yes selected for any item listed in question above please indicate if the changes are expected to negatively affect your organisation from a sales perspective

Answer	Number of Responses
N/A	2
No	13
Yes	16
Grand Total	**31**

Commentary

Under MDD, manufacturers relied heavily on equivalence data to support their clinical claims (23/31). Data to comply with MDR clinical requirements is being sourced almost equally from literature searches, clinical investigations, and post market sources. This indicates manufacturers are supplementing clinical investigations with literature and post market information where possible. This is as expected by the researcher and aligned with the experience of the researcher and the secondary research.

The data shows that the guidance documents available (MDCG 2020-5 & MDCG 2020-6) provide adequate guidance on clinical evaluation requirements and methodologies for data collection are well understood. However, the data gathered for devices under MDD is lacking for the majority of

respondents for supporting the intended purpose, indication statements and associated clinical benefits of the device(s) as well as the conditions of use and specific contraindications. This finding is aligned with the secondary research, the guidance documents are well understood but detail of how to collect sufficient data is lacking.

The data shows mixed responses for available data sufficiently covering all patient populations, all device variants and the device lifetime in use.

17/31 respondents indicate that revisions have been made to the intended purpose, Device indications have been revised to a greater extent as 22/31 indicate the device indications have been revised. 20/31 indicate the device contraindications have been revised and 22/31 indicate revisions to their risk management systems. This indicates a significant change in terms of the Instructions for Use provided for devices and the potential for exclusion of certain patient populations. It is expected as a result of these changes that residual risks will be revised. Although these impacts to the IFU are significant it is interesting to discover that the majority of respondents do not expect a resulting impact to the patients accessing the device (18/31) but 9 respondents did indicate they do expect an impact. Almost a third of respondents expect an impact to patient access which is significant.
This data indicates that to avoid costly clinical investigations, manufacturers have instead chosen to restrict the use of their devices.

Almost 50% of respondents do not expect an impact to registrations outside the EU. This can be interpreted as the clinical evidence data held by manufacturers under MDD is still deemed sufficient outside of the EU. This finding is aligned with the secondary research which indicated a reduction in patient activity in the Czech Republic but not in the US. We may see a larger reduction in devices marketed within the EU once the MDR transition period has passed.

Approximately 50% of respondents expect a reduction in sales. It can be surmised that changes in the IFU to meet clinical evidence requirements will impact sales of the device. Considering the cost to the organisation in terms of resources needed to meet MDR requirements and potential for loss of sales, the MDR places a manufacturer in an unfavourable financial position. This may lead to manufacturers withdrawing their products from the EU market and pursuing non-EU markets instead.

This data answers the research question on key compliance challenges for legacy devices, in particular, the impact of MDR clinical evidence requirements. Manufacturers relied heavily on equivalence under MDD. This data mirrors the experience of the researcher and supports the hypothesis that clinical data accepted by regulators under MDD is not sufficient to support previous MDD IFU claims made by manufacturers under MDR.
In the absence of sufficient data, manufacturers have revised the IFU which may in turn result in a loss of sales and patients accessing the devices. This also adds importance to the third objective of this study, to discover the potential impact on patients in the event of shortage.

4.2.4 OUTSOURCING OF ACTIVITIES/ BUSINESS IMPACTS

Question - Please indicate if your company has outsourced any of the following activities to fulfil MDR 2017/745 requirements:

	Yes	No	Don't Know
Technical Documentation Compilation	11	19	1
Periodic Safety Update Report Compilation	5	24	2
PRRC Role (Person Responsible for Regulatory Compliance)	3	28	/
Clinical Evaluation Report Compilation	16	14	1
Post Market Clinical Follow Up Report Compilation	5	26	/
Post Market Surveillance Activities	5	26	/
Labelling Activity	3	27	1
Internal Audits/ Self Inspection	9	22	/

Commentary

The areas showing the strongest response for outsourcing are Technical Documentation and Clinical Evaluation Report compilation. This supports the theory that demonstration of clinical evidence is a challenge for manufacturers. In relation to the research objectives, the data collected shows that key challenges for businesses in terms of outsourced supports are in the areas of Technical Documentation and Clinical Evaluation Report generation. This shows the expertise needed to compile these documents is in short supply within companies and outsourcing these activities are costly. This highlights another significant burden on manufacturers who may be facing reduced sales. It may not be cost effective for smaller organisations to retain their products on the market after the MDR transition period, some may allow their MDD certificates to expire and withdraw from the market.

4.3 INTERVIEW QUESTIONS

4.3.1 DEMOGRAPHIC INFORMATION

Age range	**Number of Interviewees**
21-25 years	/
25-35 years	1
35-45 years	5
45-55 years	3
55+ years	/
Years of experience	**Number of Interviewees**
0 - 5 years	2
5 - 10 years	3
10 - 15 years	5
15 - 20 years	1
20+ years	1
Area of expertise	**Number of Interviewees**
Medicine/ Clinician	4
Sales & Marketing	2
Medical/ Clinical Affairs	3 1 – Is also a physician
Pharmacy	1
Other	0

4.3.2 GENERAL QUESTIONS RELATING TO OSTEOARTHRITIS

Question 1 - In your experience what is the age profile of most patients suffering with mild/ moderate Osteoarthritis.

Response - OA is the most common form of arthritis that can manifest early in adulthood, frequently after age 40/ 50 years but most common in 60s. OA is possible before 45 and occasionally late 30s for athletes and those who have had physical trauma. OA is an incurable disease that can only be managed rather than cured. Globally, OA is the most prevalent condition in individuals aged over 60 years, with women (60%) affected more than men. Hormones in post-menopausal women impacts the joint health. OA progression is reliant on general health, BMI is very important and good muscle structure.

Question 2 - Can you please tell me the most prevalent joint with patients suffer?

Response - The most affected joints are the knees, hips, spine, hand (in this order) and more than one joint can be involved. Any joint can be affected but predominantly lower limbs such as knees and hips. Hip arthritis is very rare in Asian populations.

Question 3 - Can you please describe the most common symptoms patients present with?

Response - Pain usually is the symptom that forces patients to seek medical advice, stiffness is usually present early but patients will not seek advice until they feel pain. Joint pain is by far the most common OA symptom which leads to physical disability difficulty performing normal daily activities (such as climbing stairs, shopping, bending for driving the car, getting into the bath or shower etc.,). Pain can be intermittent or constant. Other possible symptoms are stiffness (above all morning stiffness) swelling and crepitus (a crunch sound when moving the joint). Besides, OA disease definition is now more accurate and includes the whole joint, involving not just cartilage, but also synovial tissue, subchondral bone, tendons, and ligaments. Therefore, there are also signs of the disease, when in advanced stage, that patients cannot refer but are detectable after radiographic examination (X-ray and MRI). Pain is a bio-psycho-social issue. Stiffness is generally higher in the morning with pain lower in the morning and in the evening, pain is higher and stiffness reduces.

Question 4 - Is reduced physical function a common complaint amongst the OA patients?

Response - OA has long been associated with loss of functionality and disability, earlier stages of the disease to a lesser degree. Pain cycle is related to rigidity in the joint and joints rubbing due to cartilage loss. OA is among the top ten leading causes of years lived with disability for adults older than 70 years, affecting one third of the people belonging to this age group. Physical function reduction is not only related to limitation in patient mobility but also involve limitation in self-care, in running usual activities and is a cause of anxiety and depression.

Question 5 - In general, how does OA impact a patient QoL?

Response - Pain is the most common complaint and the most significant cause of decreased quality of life among OA patients. Pain reduces willingness to move. The impact of OA on the quality of life is significantly associated with the sites of pain. There is a domino effect, patients may place more weight on another joint to compensate and therefore introduce an issue in other joints. Furthermore, OA is a chronic degenerative disease that affects functional ability which is a well-recognized part of ageing. Functional ability is peoples abilities to meet their basic needs to ensure an adequate standard of living. Patient experience and their expectation of activities/lifestyle is fundamental to understanding the impact for individuals. Pain is a bio-psycho-social issue. Patient circumstances have a huge impact on pain and progression of the disease, highly linked to patient mindset, coping mechanisms, and self-efficacy (willingness to manage their condition). Joint replacement is not always a great solution as pain can still exist in the joints. Loss of physical function can lead to loss of earnings. Mental health issues, social isolation and trouble sleeping can be another factor for sufferers.

4.3.3 SPECIFIC QUESTIONS RELATING TO INTRA-ARTICULAR MEDICAL DEVICES

Question 1 - Are you experienced or knowledgeable in administration of intra-articular products such as Euflexxa, Suplasyn or Synvisc?

Response - Five interviewees responded Yes and five stated although they have no practical experience but interact with physicians.

Question 2 - Do you agree these products play a key role for sufferers of mild/ moderate OA?

Response – Responses were positive for mild to moderate sufferers. By localising the site of action, reduced risk and impact to the patient. These products provide lubrication and reduce rubbing in the

joint. Intra-articular therapies play a pivotal role in the management of the disease for patients who present Kellgren and Lawrence grade 2 and 3 (mild-moderate OA). Intra-articular injection with hyaluronic acid are included in current guidelines. For example, in 2019 ESCEO algorithm for the management of knee OA, intra-articular injections with HA are suggested for those patients with severe symptoms, when other therapies (oral NSAIDs) have failed. Multimodal treatment strategy is the cornerstone for OA management and often IAHA injections are suggested in combination with SYSADOAs (symptomatic slow-acting drugs for OA) and oral NSAIDs. There is also a placebo effect to consider, invasive treatments have a greater placebo effect. Patients are looking for 30% pain relieve for chronic conditions so any improvement greater than this is a good advantage.

Two interviewees reported that it plays a role but not necessarily a key role, it really depends on the patient and what other products they can tolerate (such as steroids).

One interviewee reported speaking to a patient post injection and the report was that one-shot is very effective for reducing pain.

Question 3 - How would you describe the performance of intra-articular HA in alleviating patient discomfort?

Response – Intra-articular injections of HA are an effective and well tolerated treatment for osteoarthritis. The efficacy of one single administration can last for over 6 months for many patients. These are safe products when administered correctly in a sterile environment. Patients are essentially looking for 30% pain relieve for chronic conditions. Patients report a positive experience over steroid injections, IAHA gives greater pain relief and as a patient can move more, they relieve their stiffness and can improve musculature.

Question 4 - How would you describe your confidence in the safety of intra-articular HA products?

Response - No concerns expressed by any interviewee. Minor side effects such as local pain and swelling. Severe allergic reactions are very rare. IAHA injections are a well-tolerated medical device. Most of the possible serious adverse events can be attributed to HCP malpractice (inadequate sterilization of the site, injection outside of the synovial cavity etc) and not to the product itself. The physician must be skilled and confident, orthopedic specialists are most skilled. It was highlighted by one physician that they are aware of other doctors mixing steroids with the IAHA injection which can result in crystallization within the joint which is a safety concern. Successful administration is the greatest concern for both patients and the physicians. NSAIDs bring drawbacks and should not be used long-term (for more than 4-6 weeks). Long-term use brings side effects.

Question 5 - Would you agree that intra-articular HA products have fewer side effects compared to oral NSAIDs?

Response - All interviewees agreed. Systemic drugs (such as oral NSAIDs) should be used with caution and according to patient medical history. Dosage of NSAIDs impacts the likelihood of side effects. Well-known possible side effects of NSAIDs are impacts to gastric mucosa, renal system, cardiovascular system, hepatic system. HA intraarticular injections compared to oral NSAIDs represent a safer option in those patients (i.e. elderly and those with comorbidities). Pain at the injection site can be related to phobia but quite limited. One doctor reported no side effects other than a feeling of pressure following the injection. Corticosteroids may reduce cartilage within the joint so is not preferred as a treatment option.

Question 6- What are the most common side effects experienced by patients undergoing treatments with intra-articular HA products?

Response - Pain may be transient, but the pain is miniscule compared to OA pain. Local reactions (redness, effusion, irritation) are also reported by interviewees. In rare case there are systemic reactions such as fever, chills, or cardiovascular reactions, and in very rare cases anaphylactic reactions. Pressure has also been reported but once the patient moves around there are no issues. Infection is possible or septic arthritis but has been rare.

Question 7 - Do you feel that the improvements in QoL outweigh any potential risks of side effects associated with these products?

Response - Consensus is that benefits are higher than the potential risks. Patients will have better mobility and therefore improved QoL. Lack of movement is the biggest issue for these patients and use of these devices improve ability to move which improves QoL overall. The improvements are dependent on the patient and the experience of the treating physician, their skill is key for a positive patient experience. There is a risk of allergy as with any product.

Question 8 - In your opinion, what is the safest, most cost effective and beneficial treat for OA patients?

Response - First line treatment should be weight loss, loss of 5% body weight is recommended as most people are overweight in terms of BMI. Physical exercise is the crucial for many cases of mild OA. NSAIDs are more cost effective but brings side effects. Consensus is that control of weight is key - many patients have cardiovascular or lung issues and weight loss places less stress on the body which is beneficial overall. Patients need to be aware that the mindset of a pill for everything is not the correct mindset. As we age metabolism slows which is a contributor to weight gain and stress on the body. Women need to be more aware of the importance of a strong musculature. The rate of musculature decline is partially within a patient's control. A benign and well tolerated drug is glucosamine sulfate (in the class of SYSADOA) which can be used for very long term (studies are up to 3-year treatment) and it is considered a background treatment for knee OA. In summary, most effective for mild cases is lifestyle changes, weight loss, good nutrition. Mild-moderate OA requires medication or OA injection. One physician recommended physio as a cost-effective option.

Question 9 - Are you experienced or knowledgeable in administration of intra-articular Platelet Rich Plasma treatments?

Response - Interviewees report this as a relatively new treatment. This is a topic that generates a lot of interest, but it is debatable whether it is effective or not. PRP injections still represent the so-called alternative treatment but is an expensive option. There are positive signals that PRP may also lead to improvement of OA symptoms, but existing studies present high level of variability in preparation methods, making their comparison difficult. So far, PRP injections are not mentioned in any OA guidelines. There are no products that are disease modifying that are non-toxic so the expected effect will be modest at best.

One interviewee is experienced in PRP treatments, but this is most commonly used for treating injuries in competitive athletes. This physician commented this is not their preferred course of treatment.

Question 10 - Do you think an implant card is beneficial for this type of product?

Response – The responses were mixed for this question. An Implant card might be very helpful for medical devices that persists in human body for longer period. May be useful for traceability or when patient literacy is low. An opinion is that it may be an administrative barrier and will lead to physicians

moving to other interventions. Implant cards for patients may be challenging for multiple treatments, a patient presenting 5 implant cards on administration to hospital could lead to confusion. Some reported it is not necessary for HA based products, the task to record the information should be on the physician performing the injections.

4.3.4 QUESTIONS RELATED TO PATIENT IMPACT IN THE EVENT OF MARKET SHORTAGE

Question 1 - What impact would it have for patients in the event intra-articular HA products were in short supply in the market?

Response – The primary response is that patients will miss one of the most utilized treatments for osteoarthritis with a risk of reverting to other oral treatments to look for pain alleviation. In general, patients using IA HA are not eligible for other treatments due to other health issues. Many patients will request treatment prior to travel or social events, and it will severely impact their comfort. The patient may not be able to take NSAIDs as they may have gastric issues. Patients reverting to NSAIDs may experience greater side effects and less relief (NSAIDs may have been used prior to injections as the NSAIDs were not providing sufficient relief). This might cause an increase of side effects and a higher burden in terms of costs to the National Health Systems. Patients may resort to opioid usage which is a negative. A break in the regimen would impact patient as the joint needs continuous treatment.

One reported that it is important but not medically vital as patient responses are quite individual. It is likely that physicians will move to an alternative IA HA product.

One reported there would not be a massive impact as physicians would resort to physio or non-injectable options.

Question 2 - In the event of lack of supply, what would be the impact to existing users QoL?

Short-term short supply may not be a huge issue but could be a big issue for patients not eligible to take NSAIDs or those who will not remember to take an NSAID or have dexterity due to age (may have difficulty opening bottles etc.,). HA is more beneficial as the HCP can manage the administration. This treatment is more important for patients that get greater relief from these products. Disease progression could speed up without the products. QoL will decrease since the functional ability will be seriously affected, limiting social activities but also possibly affecting work environment (absenteeism) as well. Depression for patients may also become a factor. One reported not a massive impact as physicians would resort to physio or non-injectable options. Steroids may be used provided low quantities of local anesthetics can be used as it is chondro-toxic and should be avoided.

One reported that corticosteroids may be used as an alternative which will provide relief but will progress the disease faster.

SUMMARY

Questionnaire respondents mainly agreed they understand requirements related to the MDR requirements such as Notified Body Scrutiny procedures, Economic Operator registration, EUDAMED, Technical documentation, Vigilance, PMS, UDI, Labelling and GSPRs. Respondents indicate that Supply Chain scrutiny has been a challenge for their organization. This is an area not predicted by the researcher and not identified in the course of the secondary research.

In terms of the research objectives key compliance challenges are clear with respect to Technical Documentation preparation, with the vast majority agreeing that this has been challenging from both cost and labour perspectives. The data also shows 25 respondents report an increase in personnel needed for their organisation.

Although respondents agree that there is sufficient time allowed for transition to MDR the responses indicate that there is not sufficient support from regulatory agencies in terms of guidance provided, only 8 responses were positive in this regard.

This is aligned with the hypothesis of the researcher, the transition period is sufficient but there is a lack of support from regulatory agencies for specific groups of devices.

The data collected through questionnaires answers the research question on key compliance challenges for legacy devices, in particular, the impact of MDR clinical evidence requirements. Manufacturers relied heavily on equivalence under MDD. This data mirrors the experience of the researcher, the secondary research and supports the hypothesis that clinical data accepted by regulators under MDD is not sufficient to support previous MDD IFU claims made by manufacturers under MDR.

In the absence of sufficient data, manufacturers have revised the IFU which may in turn result in a loss of sales and patients accessing the devices. This also adds strength to the third objective of this study, to discover the potential impact on patients in the event of shortage.

The interviews serve to answer research objective 3 which was to discover the potential impact on patients in the event of market shortage. The findings of the research can be summarized as follows:

- Intra-articular medical devices play a role in the management of the disease for patients with mild- moderate OA.
- Intra-articular injections of HA are an effective and well tolerated treatment for osteoarthritis. Patients report a positive experience over steroid injections, IAHA gives greater pain relief and as a patient can move more, they relieve their stiffness and can improve musculature.
- Physicians have confidence in the safety of these devices, the greatest risks are from injection technique rather than the device itself.
- Intra-articular HA products have fewer side effects compared to oral NSAIDs.
- Post injection pain is the most reported side effect and is generally transient, this pain is described as miniscule compared to OA pain.
- These products improve patient mobility and therefore improve QoL.
- PRP treatment is an alternative for OA management but not used widely in practice.
- Implant card may be useful for this product.
- Patients using IAHA are not eligible for other treatments due to other health issues such as gastric issues. Patients reverting to NSAIDs may experience greater side effects and less relief (NSAIDs may have been used prior to injections as the NSAIDs were not providing sufficient relief). This might cause an increase of side effects and a higher burden in terms of costs to the

National Health Systems. Patients may resort to opioid usage which is a negative. A break in the regimen would impact patient as the joint needs continuous treatment. Disease progression could speed up without the products. QoL will decrease since the functional ability will be seriously affected, limiting social activities but also possibly affecting work environment (absenteeism) as well. Depression for patients may also become a factor. One reported not a massive impact as physicians would resort to physio or non-injectable options.

The findings of the interview were aligned with those of the secondary research:

- IAHA is in common use for OA management.
- IAHA is regarded as a safe and effective treatment for OA Management.
- HCPs have confidence in the product even though clinical evidence is lacking.
- Clinical evidence for PRP treatments is also lacking.

Overall, intra-articular HA injections present a positive improvement in QoL, particularly for those who are ineligible for NSAIDs. A short-term supply issue may not be a significant for patients but will have the greatest impact on patients who get greatest relief from them. Patients reverting to NSAIDs will be prone to more side effects linked to NSAIDs which may place a corresponding burden on the Health Care system.

CHAPTER 5: RESEARCH CONCLUSION

RESEARCH CONCLUSIONS

5.1 BASED ON THE MAIN RESEARCH OBJECTIVES

The objectives of this study were as follows:

1. Examine key MDR 2017/ 745 compliance challenges for legacy devices, in particular, the impact of MDR clinical evidence requirements.

2. Compare current EU MDR 2017/745 framework versus US medical device regulatory framework and pharmaceutical product requirements with respect to clinical data.

3. Discover potential patient impact in the event of market shortage for implantable, intra-articular medical devices.

4. Propose possible routes forward for industry and regulators to ensure continuity of supply of implantable, intra-articular medical devices.

It is evident that under MDD, manufacturers relied heavily on equivalence data to support their clinical claims. Equivalence is no longer permitted under MDR 2017/745 unless all original clinical data can be sourced from the claimed product which leads to the question of contracts, intellectual property and availability of such. The data to comply with MDR clinical requirements is being sourced by manufacturers almost equally from literature searches, clinical investigations, and post market sources.

The data shows that the guidance documents available (MDCG 2020-5 & MDCG 2020-6) provide adequate guidance on clinical evaluation requirements and methodologies for data collection have been well-understood by industry but the data available (and generated under MDD) will not support the intended purpose, indication statements and associated clinical benefits of the device(s) as well as the conditions of use and specific contraindications in may cases.

The data shows mixed responses for available data sufficiently covering all patient populations, all device variants and the device lifetime in use. As a result, revisions have been made in over half of cases to intended purpose, indications, contraindications and risk management systems. This shows a significant change in terms of the Instructions for Use provided for devices and the potential for exclusion of certain patient populations. Manufacturers are opting to revise claims to avoid costly clinical investigations.

Although these impacts to the IFU are significant it is interesting to discover that the majority of respondents do not expect a resulting impact to the patients accessing the device, this raises the question will there be greater incidence of off-label use? For physicians using these products for a long time, will they read the updated IFU? This is an interesting topic that could be explored as a separate study.

Data to comply with MDR clinical requirements is being sourced almost equally from literature searches, clinical investigations, and post market sources. Respondents agree that clinical evaluation requirements are well-expressed in guidance documents. Clinical evidence gathered for devices under MDD is lacking resulting in revisions to intended purpose, indication statements and associated clinical benefits of the device(s), the conditions of use, specific contraindications, and risk management files. A third of surveyed manufacturers expect a decrease in patients accessing the device and 50% expect a reduction in sales. The data collected reinforces the findings of the secondary research, the area of clinical evidence is an area of difficulty for manufacturers.

Interestingly, the revisions to device claims are not expected to affect markets outside of the US. It can be surmised that the MDR has introduced more stringent requirements than other markets such as the US, Canada and Japan.

Research objective 2 includes a review of the current EU MDR framework versus US medical device and pharmaceutical products. This review determines that the EU framework has become more stringent than the US framework. The EU has now become a more challenging market to access than the US. This is the inverse of the MDD versus US framework and the change is down to the FDA system allowing for grandfathering and claiming substantial equivalence, this concept of equivalence is no longer permitted in the EU unless certain caveats are met. Clinical data requirements are more prescriptive in the pharmaceutical industry. For medicinal product clinical trials, it is well known that blinded RCTs are the preferred approach. Adoption of this methodology for medical devices is often impossible - a placebo may also be unethical and expose a patient to unnecessary risk.

Approximately 50% of respondents expect a reduction in sales. It can be drawn from this that changes in the IFU to meet clinical evidence requirements will impact sales of the device. One interviewee highlighted off-label use during the discussion, based on his experience with the device, the physician uses the device in joints not prescribed by the manufacturer. Based on the significant changes made to the IFU by the manufacturer, there is a predicted reduction in sales. The magnitude of the drop in sales may not be as significant as expected if physicians use the product off-label. Of course, this is not an optimal situation.

Another interesting area that could be explored as a separate study is the area of osteoarthritis in post-menopausal women and the public of this. I think knowledge of the disease within this demographic group could be lacking. We are all aware of the importance of a healthy body weight and good musculature but is it really understood the link between these factors, the impact of menopause on female musculature and the disease prevalence?

A review of the secondary research highlights that innovators in the PRP field may struggle to place PRP products on the market under the MDR. Maresova et. al., (2020), addressed this point, which was reinforced during the interviews - the clinical experts were interested in these products but unconvinced of their effectiveness based on clinical data available. This raises an interesting observation – MDR is a challenge for legacy treatments for OA and may be presenting a barrier to innovative products also. This limits patient access to products even further.

Through the secondary research, it was identified through extensive literature review by Migliore et. al., (2016), that legacy devices, are lacking in clinical evidence. This point is reinforced by the primary research, the questionnaire data confirms reliance on data from sources other than clinical investigations. The study Migliore et. al., (2016) recommends brand-specific studies to aid clinician decision-making. This study also raises the question of clinician understanding of these products and

confidence in these products. Clinician understanding has been confirmed through the primary research, the interviewed clinicians are knowledgeable of the products, use and safety. The idea for collaborative studies leads the researcher to a possible route forward for industry and regulators.

5.2 RESEARCH LIMITATIONS:

The main limitation to consider in this research was the small sample size, the research was quite limited in terms of access to experts in this area. If I was embarking on this project again, I would have included interviews with QA and RA experts. Although the questionnaire responses were very valuable and served to answer the key questions, a semi-structured interview would have allowed me to delve further into the topic.

5.3 FINAL CONCLUSIONS:

The MDR brings may positives, particularly for the patient and it is undisputed that patient safety is at the forefront of our industry. Introduction of requirements such as Supply Chain traceability, UDI and SSCP are essential to protect patients. This was the goal of the MDR. There are many lessons to be learned from past scandals, but it seems the industry as a whole is not ready for the stringent clinical evaluation requirements. The clinical requirements are well expressed in regulatory texts, but they do not answer the real questions – how much data is enough data and how can we bridge the gap in data between MDD and MDR in a practical way? The regulators are not in a position to support manufacturers with this information, this raises a further question – are the regulators struggling with this topic too?

With the best of intentions, has the MDR moved too far, too fast for industry and regulators?

As a result of the cost to organisations in terms of resources needed to meet MDR requirements and potential for loss of sales, the MDR places a manufacturer in an unfavourable financial position. This may lead to manufacturers withdrawing their products from the EU market and pursuing other markets outside of this territory. The knock-on effect for patients using intra-articular medical devices for Osteoarthritis treatment will be of significance for those who are ineligible for NSAIDs when physical therapy, basic pharmacological treatment, and first-line joint injection with corticosteroid have not given adequate relief. MDR may also be presenting a barrier to newer therapies such as PRP, primary and secondary research has shown that although there is interest from the medical profession, there is little clinical data available. Again, perhaps MDR has moved too far, too fast.

The transition period for Class III implantable intra-articular devices ends in May 2027, we may then see a decline in these products available on the EU market and a delay in innovative products reaching the market. Considering the prevalence of OA within society and the progressive nature of the disease, the impact of the MDR may be significant for patients who rely on these products to positively affect their QoL.

5.4 RECOMMENDATIONS

Research objective 4 was to propose possible routes forward for industry and regulators to ensure continuity of support. The data collected shows that MDR requirements are well understood but there is a lack support from regulators. In some respects, the MDR has gone too far and too fast for legacy

devices. Lessons ought to be learned from the mistakes of the FDA in terms of allowing for grandfathering in but I believe that a solution is possible via the EUDAMED database. The Clinical module could be expanded to allow data sharing by manufacturers of particular product groups (based on MDA/MDN, MDT and MDS codes). The MDA / MDN-codes are based on product design and intended purpose, and as a result are linked to the designation of suitably qualified Notified Body reviewers.

Use of these codes in EUDAMED for information sharing would allow for sharing of information relevant to the correct product groups. In the case of IAHA medical devices, the appropriate MDN code is MDN 1102. Manufacturers of these products could voluntarily and potentially anonymously (by redacting brand names) add the data relevant to this code. Sharing data in this manner could allow manufacturers to leverage off data from equivalent and similar products using a collaborative approach. This could allow manufacturers to claim equivalence on the basis technical characteristics, biological characteristics and clinical characteristics by using the MDT and MDS codes to describe the products. This would allow for data sharing based on similarity without the need for costly legal agreements between manufacturers to allow data sharing. This would enhance patient safety also by improving manufacturer knowledge. Claiming equivalence in this way could lessen the burden on manufacturers in terms of sufficient clinical evidence, this in turn will reduce the potential for market shortages. This approach could also allow manufacturers retain their previous MDD claims provided data shared is robust enough to support. This solution could be a way to bridge the gap between old and new requirements.

This is a point I raised with EUDAMED but it was communicated to me that it is not planned at this time.

I believe there is an opportunity for the MDA/MDN, MDT and MDS codes to be used for more than simply categorisation of products by Notified Bodies.

REFERENCES AND BIBILIOGRAPHY

Behan, R, Watson, M, Pandit, A (2020) Molecular Medicine Ireland, Dublin, Ireland, CÚRAM – Centre for Research in Medical Devices, Galway, Ireland, *New EU medical device regulations: Impact on the MedTech sector* Available at: https://www.researchgate.net/publication/324963773_New_Eu_medical_device_regulations_Impact_on_the_medtech_sector

Billesberger, L, Fisher,K. Qadri,Y, Boortz-Marx, R (2020) Hindawi Pain Research and Management Volume 2020, Article ID 3873098, *Procedural Treatments for Knee Osteoarthritis: A Review of Current Injectable Therapies* Available at: *https://pubmed.ncbi.nlm.nih.gov/32148599/*

BMJ 2012; 345 doi: https://doi.org/10.1136/bmj.e4560 (Published 03 July 2012)Cite this as: *BMJ* 2012;345:e4560

Clemens, N (2018), The European Medical Device Regulation 2017/745/EU: Changes and Impact on Stakeholder *Journal of Clinical Research best practices, Vol. 14, No. 9* Available at: https://www.researchgate.net/publication/327337806_The_European_Medical_Device_Regulation_2017745EU_Changes_and_Impact_on_Stakeholders

Kawano MM, Araújo IL, Castro MC, Matos MA. Assessment of quality of life in patients with knee osteoarthritis. Acta Ortop Bras. 2015 Nov-Dec;23(6):307-10. doi: 10.1590/1413-785220152306150596. PMID: 27057143; PMCID: PMC4775507.

Kearney, B, McDermott, O (2023), Therapeutic Innovation & Regulatory Science, *The Challenges for Manufacturers of the Increased Clinical Evaluation in the European Medical Device Regulations: A Quantitative Study* Available at: https://pubmed.ncbi.nlm.nih.gov/37198369/

Maresova, P, Hajek,L, Krejcar, O, Storek, M, Kuca, K (2020) MDPI Administrative Science*, New Regulations on Medical Devices in Europe: Are They an Opportunity for Growth?* Available at: https://www.researchgate.net/publication/350459225_New_Regulations_on_Medical_Devices_in_Europe_Are_They_an_Opportunity_for_Growth

Maheu E, Rannou F, Reginster JY. Efficacy and safety of hyaluronic acid in the management of osteoarthritis: Evidence from real-life setting trials and surveys. Semin Arthritis Rheum. 2016 Feb;45(4 Suppl):S28-33. doi: 10.1016/j.semarthrit.2015.11.008. Epub 2015 Dec 2. PMID: 26806183.

Medical Device Co-ordination Group (2020), *MDCG 2020-5 Clinical Evaluation – Equivalence - A guide for manufacturers and notified bodies April 2020* Available at: https://health.ec.europa.eu/system/files/2020-09/md_mdcg_2020_5_guidance_clinical_evaluation_equivalence_en_0.pdf

Medical Device Co-ordination Group (2020), *MDCG 2020-6 Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC A guide for manufacturers and notified bodies April 2020* Available at: https://ec.europa.eu/docsroom/documents/40904?locale=de

Medical Device Co-ordination Group (2021), *MDCG 2021-25 Regulation (EU) 2017/745 - application of MDR requirements to 'legacy devices' and to devices placed on the market prior to 26 May 2021 in accordance with Directives 90/385/EEC or 93/42/EEC October 2021* Available at: https://health.ec.europa.eu/system/files/2021-10/md_mdcg_2021_25_en_0.pdf

Medical Device Co-ordination Group (2021), *MDCG 2021-6 Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation April 2021* Available at: https://health.ec.europa.eu/system/files/2021-04/mdcg_2021-6_en_0.pdf

Migliore, A, Bizzi, E, De Lucia, O, Delle Sedie, A, Bentivegna ,M, Mahmoud, A, Foti, C (2016) Libertas Academica *Differences among Branded Hyaluronic Acids in Italy, Part 1: Data from In Vitro and Animal Studies and Instructions for Use* Available at: https://pubmed.ncbi.nlm.nih.gov/27257398/

Pavone,V, Vescio,A, Turchetta,M, Chiara Giardina,S. Culmone, A, Testa, G (2021)Section of Orthopaedics, Department of General Surgery and Medical Surgical Specialties, A.O.U. Policlinico Rodolico – San Marco, University of Catania, Catania, Italy *Injection-Based Management of Osteoarthritis of the Knee: A Systematic Review of Guidelines* Available at: *https://pubmed.ncbi.nlm.nih.gov/33959026/*

Rosen, J, Niazi, F, Dysart, S (2020), Advanced Therapy *Cost-Effectiveness of Treating Early to Moderate Stage Knee Osteoarthritis with Intra-articular Hyaluronic Acid Compared to Conservative Interventions* Available at: https://pubmed.ncbi.nlm.nih.gov/31735982/

Smirthwaite. A (2021), BSI White Paper, *Clinical evaluation under EU MDR* Available at: https://www.bsigroup.com/globalassets/localfiles/en-gb/medical-devices/whitepapers/clinical-evaluation-white-paper/clinical-evaluation-under-eu-mdr.pdf

The Irish Times, Nov 25 2018, Suspect device: the all-metal hip replacement that caused untold hardship

Zargar N, Carr A. The regulatory ancestral network of surgical meshes. PLoS One. 2018 Jun 19;13(6):e0197883. doi: 10.1371/journal.pone.0197883. PMID: 29920525; PMCID: PMC6007828.

Section 1 Topic and Objectives

To identify, define and describe the regulatory burden of Regulation 2017/745 placed on manufacturers of legacy implantable, intra-articular medical devices for treatment of Osteoarthritis and the potential impact of market shortages as manufacturers strive to comply.

Legacy implantable intra-articular devices such as Durolane®, Hyalgan® and Synvisc® have been available on the European market under the Medical Device Directive 93/42/EEC. Additionally, these devices have been available on the US market for many years and according to the FDA PMA Database, Durolane and Synvisc were granted PMA approval in 2017.

These devices contribute to an improved quality of life for Osteoarthritis sufferers. Viscosupplementation (injection of hyaluronic acid into affected joints) is recommended for patient with symptomatic mild to moderate Osteoarthritis who have not benefited sufficiently from non-pharmacological treatment and analgesics/ NSAIDs or are unable to take analgesics/ NSAIDs.

Osteoarthritis is a disease occurring mainly in adults over 50 years of age and results in reduced quality of life. Osteoarthritis is a disorder of synovial joints. Some complications of the disease include difficulty walking, performing day-to-day tasks, chronic pain and mental health issues resulting from the physical challenges and pain suffered by patients.

The aim of this study is to identify specific barriers to MDR (Medical Device Regulation 2017/745) certification for manufacturers of the above-mentioned devices and evaluate the impact on patient quality of life in the event manufacturers cannot meet the new requirements.

The objectives of this study are as follows:

1. Examine key MDR 2017/ 745 compliance challenges for legacy devices, in particular, the impact of MDR clinical evidence requirements.

2. Compare current EU MDR 2017/745 framework versus US medical device regulatory framework and pharmaceutical product requirements with respect to clinical data.

3. Discover potential impact on patients in the event of market shortage for implantable, intra-articular medical devices.

4. Propose possible routes forward for industry and regulators to ensure continuity of supply of implantable, intra-articular medical devices.

This topic is linked to the Medical Device Quality Systems and Regulation module.

Section 2 Literature Review

The MDD (Medical Device Directive 93/42/EEC) and AIMD (Active Implantable Medical Device Directive 90/385/EEC) have been repealed and replaced by MDR 2017/745.

MDR 2017/745 places a significant regulatory and financial burden on medical device manufacturers as they strive to meet the new requirements. In contrast to the US regulatory scheme there are no provisions for grandfathering products certified under the previous Directives.

It is important to note that no requirements of the previous directives have been removed; the MDR only adds further requirements.

Some of the main changes introduced by the MDR are listed below.

- Registration of Notified Bodies and Economic Operators
- New Technical Documentation requirements
- New Notified Body scrutiny procedures for higher risk devices
- New labelling requirements (including implant cards)
- New requirements for Clinical Investigation and evaluation
- Introduction of Unique Device Identification (UDI)
- Introduction of EUDAMED Database and placement of manufacturers information in this database

Although the requirement for clinical evidence is not new, the MDR introduces the term 'clinical data' in Article 2 (48).

'Clinical data' means information concerning safety or performance that is generated from the use of a device and is sourced from the following:

— clinical investigation(s) of the device concerned,

— clinical investigation(s) or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated,

— reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated,

— clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up;

Guidance documents MDCG 2020-5 (Guidance on clinical evaluation – Equivalence) and MDCG 2020-6 (Guidance on sufficient clinical evidence for legacy devices) indicate that the clinical evaluation must show, through scientifically sound and objective evidence that the device meets its intended use, has clinical benefit and that the benefit-risk ratio when compared to other options is acceptable. For Class III devices a Clinical Evaluation Report (CER) is still required but the requirements for the content of these reports has changed. According to Part A of Annex XIV (Clinical Evaluation) manufacturers must, plan, conduct and document clinical evaluations on a continuous basis.

MDR Article 61(1) states: *Confirmation of conformity with relevant general safety and performance requirements set out in Annex I under the normal conditions of the intended use of the device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit-risk ratio referred to in Sections 1 and 8 of Annex I, shall be based on clinical data providing sufficient clinical evidence, including where applicable relevant data as referred to in Annex III. The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose. To that end, manufacturers shall plan,*

conduct and document a clinical evaluation in accordance with this Article and Part A of Annex XIV.

All Class III and implantable devices require clinical data from clinical investigation conducted in accordance with Good Clinical Practice.

Manufacturers operating in the EU must comply with these requirements as 'grandfathering in' is not permitted.

Transitional provisions have been set out under Article 120 of MDR 2017/745 to minimise the risk to market supply.

In summary, Article 120 states the following with respect to certification of legacy devices.

All certificates issued prior to 25/05/17 in accordance with Directives 90/385/EEC and 93/42/EEC will remain valid until the expiry date of the certificate; this period cannot exceed a maximum of five years. The exception to this is certificates issued in accordance with Annex 4 and Annex IV of Directive 90/385/EEC or Directive 93/42/EEC respectively - these certificates will expire on 27/05/22 at the latest.

There are conditions that apply to manufacturers holding certificates issued under the regulation. The devices certified may only be placed on the market during the transitional period provided there are no significant changes made to the product intended purpose of design. MDR requirements related to PMS, vigilance, market surveillance, registration of economic operators in EUDAMED and also device registration applies.

MDCG Guidance Document 2021-25, (Regulation (EU) 2017/745 – Application of MDR requirements to legacy devices and devices placed on the market prior to 26 May 2021 in accordance with Directives 90/385/EEC or 93/42/EEC), outlines requirements pertinent to legacy devices. This document defines legacy devices as those placed on the market before 26 May 2021 under the directives. Key MDR requirements relevant to legacy devices are discussed in this document.

1. MDR Post-market surveillance and vigilance requirements apply
2. Notified Bodies must continue surveillance activities under the relevant Directive. This activity can cease at the end of the validity period of the certificate issued under the Directive.
3. PSURs (Periodic Safety Update Reports) are required in accordance with MDR Article 86

In addition to highlighting applicable MDR requirements the document also highlights non-applicable requirements. Articles 15, 16 (3) & (4), 18, 25, 27 and 32 are listed as non-applicable.

Regulatory Texts

Year	Author	Title	Aims & Methodology	Conclusions
2020	Medical Device Co-Ordination Group	MDCG 2020-5 Clinical Evaluation – Equivalence - A guide for manufacturers and notified bodies April 2020	This guidance document aims to explain demonstration of equivalence to an existing on-market product for the purpose of obtaining CE certification under MDR. The document achieves this by analyzing differences between MEDDEV 2.7/1 rev.4 and MDR requirements.	This document included as it is key for understanding the MDR requirements related to claiming equivalence to other on market products. The document explains equivalence in terms of technical characteristics, Biological characteristics and Clinical characteristics. Manufacturers must present scientific justification for any differences in characteristics when claiming there are no significant differences Scientific justifications shall be provided for the different characteristics when claiming no clinical difference in safety and performance.
2020	Medical Device Co-Ordination Group	MDCG 2020-6 Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC A guide for manufacturers and notified bodies April 2020	This document aims to provide guidance for Notified Bodies and manufacturers on providing clinical evidence to fulfil the requirements of the relevant General Safety and Performance Characteristics of the MDR. This document aims to provide guidance for manufacturers and notified bodies to prepare for the conformity assessment procedure according to the MDR. The guidance document discusses Articles 6.1 – 6.5 of MDR Annex XIV Part A Section 1 and provides an explanation of the requirements.	The document is included as it provides a framework for manufacturers to prepare a clinical evaluation. Although the document highlights the GSPRs and clinical data required it is limited as it does not provide guidance on the methodology that should be used to collect sufficient clinical evidence. It is also limited as it does not provide guidance for different classes of device or technology groups. The guidance document provides a framework for Notified Bodies and manufacturers to prepare a clinical evaluation.

2021	Medical Device Co-Ordination Group	MDCG 2021-25 Regulation (EU) 2017/745 - application of MDR requirements to 'legacy devices' and to devices placed on the market prior to 26 May 2021 in accordance with Directives 90/385/EEC or 93/42/EEC October 2021	This document aims to provide guidance on MDR requirements that apply to legacy devices placed on the market under the directives. MDCG analyses the requirements laid out in Chapter VII of the MDR and their applicability to legacy devices.	This guidance document is selected as it is specifically written as a guide for legacy device manufacturers. This document concludes that MDR requirements pertinent to PMS, Vigilance, Market Surveillance, Economic Operators and PSUR apply for legacy device manufacturers.
2021	Medical Device Co-Ordination Group	MDCG 2021-6 Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation April 2021	This document is intended to answer questions of sponsors of clinical investigations carried out for the purpose of CE marking under MDR.	The document highlights the process for conducting a clinical investigation but does not provide a methodology that should be used to collect sufficient clinical evidence. The document serves to define the differences between MDR and the previous directives, explain terms such as clinical evidence, clinical performance, clinical benefit and outlines the process for conducting a clinical investigation.

2021	Smirthwaite. A	Clinical evaluation under EU MDR	This white paper provides and overview of how requirements for clinical evaluation of medical devices have evolved over time. This paper analyses the requirements defined in Article 61(1) of the EU MDR to define the process of clinical evaluation.	This white paper is focused on the purpose of clinical evaluation and describes the process of clinical evaluation. This paper is included as it describes the clinical evaluation process but is limited as it does not describe a methodology for gathering sufficient clinical evidence.

Academic Articles & Studies

Year	Author	Title	Aims & Methodology	Conclusions
2016	Migliore, A, Bizzi, E, De Lucia, O, Delle Sedie, A, Bentivegna ,M, Mahmoud, A, Foti, C	Differences among Branded Hyaluronic Acids in Italy, Part 1: Data from *In Vitro* and Animal Studies and Instructions for Use	The aim of this study is to identify scientific evidence from studies conducted on intra-articular hyaluronic acid products available on the Italian market. This study also reviews the IFUs of the available products to determine the accuracy of information given considering the scientific evidence available.	The study concludes that these on market devices are lacking in scientific evidence and recommends brand-specific studies are conducted to aid clinician decision making. This study is valuable as it indicates that the existing products, which are legacy devices are lacking in clinical evidence. The recommendation for brand-specific studies to aid clinician decision making raises a question around clinician understanding and confidence in these products that will be incorporated into the primary data collection for this dissertation.

2018	Clemens, N	The European Medical Device Regulation 2017/745/EU: Changes and Impact on Stakeholders	This journal reviews the main changes introduced by the MDR relevant for Economic Operators and Notified Bodies.	This journal is included as it details a comprehensive list of new requirements for both Notified Bodies and Economic Operators. It concludes that both Economic Operators and Notified Bodies have a significant task to undertake in order to meet the requirements of the regulation.
2020	Billesberger, L, Fisher,K. Qadri,Y, Boortz-Marx, R	Procedural Treatments for Knee Osteoarthritis: A Review of Current Injectable Therapies	This study determines the prevalence of knee OA in the Canadian region and discusses current available treatment options for patients. The study reviews current available treatments and their categorization according to various expert groups in the OA field.	The study concludes that although PRP (platelet rich plasma) therapy is beginning to replace HA injections and corticosteroids, larger trials are required to confirm the safety and efficacy of this treatment.
2020	Behan, R, Watson, M, Pandit, A	New EU medical device regulations: Impact on the MedTech sector	This article aims to compare the MDR to the previous Directives and discusses the impact in the Irish MedTech industry**.** The information sourced by CÚRAM is gathered from the Irish MedTech sector.	The article concludes that the introduction of the MDR brings challenges for manufacturers in terms of gathering clinical evidence, supply chains, Quality Management System upgrades. The article also highlights that these changes may be costly and labour intensive. The article is included as it succinctly distinguishes between the requirements of the directives and the MDR. The article is limited as it is focused on innovative products rather than legacy products.

2020	Maresova, P, Hajek,L, Krejcar, O, Storek, M, Kuca, K	New Regulations on Medical Devices in Europe: Are They an Opportunity for Growth?	This study seeks to examine the medical device industry in the Czech Republic versus other global markets in relation to medical device innovation and MDR. It closely examines barriers to innovation that come with regulation. The study aims to review production issues associated with compliance requirements particularly for innovative products. The study is based on statistical surveys from international organizations such as OECD and WHO	The study concludes that regulation in the EU has led to reduced patent activity in the Czech Republic. In contrast, there has been no decline in patent activity in the US. This information is valuable as it points to EU regulation being a barrier to innovation, this is not necessarily the case in the US. The struggles faced by legacy device manufacturers seems to be comparable to that of innovative firms.
2020	Rosen, J, Niazi, F, Dysart, S	Cost-Effectiveness of Treating Early to Moderate Stage Knee Osteoarthritis with Intra-	The study reviews the cost effective-ness of treating knee OA sufferers with High Molecular Weight HA versus Low Molecular Weight HA stage of OA. This study employs analytic models to determine responsive rate to	This study concludes the High Molecular Weight combined with physical therapy is a cost-effective treatment option for patients suffering with mild to moderate OA.

		articular Hyaluronic Acid Compared to Conservative Interventions	treatments at varying stages of the disease. The models compare treatment response rates against the cost per quality adjusted life year.	
2021	Pavone,V, Vescio,A, Turchetta,M, Chiara Giardina,S. Culmone, A, Testa, G	Injection-Based Management of Osteoarthritis of the Knee: A Systematic Review of Guidelines	This study aims to collect international guidelines to provide a comprehensive overview of injectable treatments for knee OA.	The study concludes that the effectiveness of corticosteroids is short-lived but High Molecular Weight HA injections provides a positive outcome for patients over a course of injections. This study is included as it strengthens the stance that intra-articular injections of hyaluronic acid are an effective treatment for knee OA.
2023	Kearney, B, McDermott, O	The Challenges for Manufacturers of the Increased Clinical Evaluation in the European Medical Device Regulations: A Quantitative Study	The aim of this study is to determine the impact of increased clinical evaluation requirements on medical devices manufacturers. This study uses a quantitative survey gathering responses for 68 individuals working in the medical device industry in either QA or RA roles.	The study concludes that the main source of reactive PMS data collected by manufacturers is complaints and the main source or proactive data is from PMCF. The investigation concludes that the greatest challenge to manufacturers is understanding the volume of data needed to generate sufficient clinical evidence and also a lack of transparency in Notified Body expectations. The report highlights the challenges for manufacturers and the potential for market shortage.

Gaps in the literature

A potential gap from reviewing current literature is the lack of guidance and regulation for specific groups of legacy devices, particularly in the area of clinical evidence. Legacy devices are medical devices covered by a valid certificate under the existing Directives and can continue to be placed on the market after the date of application of the incoming MDR or IVDR. The definition of a legacy device applies to general medical devices, active implantable medical devices (AIMDs), and *in vitro* diagnostic medical devices (IVDs).

Although guidance is available for legacy devices, there is no specific guidance for product groups that have been on the market for many years with little or no evolution in their design. Due to their existence in the market for a long period, the manufacturers have a significant amount of data pertaining to safety from the market.

According to Migliore et. al., (2016), there are several IA preparations currently available on the European market - Artz®, Durolane®, Hyalgan®, Hymovis®, Ostenil®, Synvisc®, and Synvisc-One®. Studies by Pavone et. al., (2021), and Billesberger et. al., (2020) support hyaluronic acid based, intra-articular devices in OA management. These devices contribute to improving the quality of life of Osteoarthritis sufferers, but manufacturers may not have sufficient clinical data to support the General Safety and Performance Requirements of MDR 2017/745.

Medical Device Co-ordination Groups have published guidance documents to assist manufacturers, but a common theme can be seen upon review of these documents, a lack of guidance on how manufacturers can collect sufficient clinical evidence.

MDCG 2020-6 (2020), provides a framework for manufacturers to prepare a clinical evaluation. Although the document highlights the GSPRs and clinical data required it is limited as it does not provide guidance on the methodology that should be used to collect sufficient clinical evidence. It is also limited as it does not provide guidance for different classes of device or technology groups.

MDCG 2021-6 (2020), highlights the process for conducting a clinical investigation but does not provide a methodology that should be used to collect sufficient clinical evidence.

This finding is further supported by Kearney & McDermott (2023), who conclude that the greatest challenge to manufacturers is determining the volume of data required to demonstrate sufficient clinical evidence. The study identifies the lack of literature published in relation to MDR clinical evaluation.

Maresova et. al., (2020) determines that EU regulation has led to reduced patent activity in the Czech Republic. In contrast, there has been no decline in patent activity in the US. This information is valuable as it points to EU regulation being a barrier to innovation, this is not necessarily the case in the US. The struggles faced by legacy device manufacturers seems to be comparable to that of innovative firms. It also highlights a larger problem, if legacy device manufacturers are unable to comply with MDR and innovative products cannot reach the market, patient options become extremely limited.

Studies by Pavone et. al., (2021), and Billesberger et. al., (2020) support and re-inforce the need for HA injections for OA management. Rosen et. al., (2020) confirms High Molecular Weight HA is cost effective in treating patients with mild to moderate OA, this supports the

products as an effective treatment option. Billesberger et. al., (2020) concludes that although PRP (platelet rich plasma) therapy is beginning to replace HA injections and corticosteroids, larger trials are required to confirm the safety and efficacy of this treatment. Based on the findings of Maresova et. al., (2020), innovators in the PRP field may struggle to place PRP products on the market under the MDR.

An interesting point is raised by Migliore et. al., (2016). Through extensive literature review they determined that 'already on market' products, which are legacy devices, are lacking in clinical evidence. The study recommends brand-specific studies to aid clinician decision-making. This study also raises the question of clinician understanding of these products and confidence in these products. This question will be incorporated into the primary data collection for this dissertation.

Section 3 Primary Research

Review of current literature highlights a gap in available guidance on a methodology that should be used to collect sufficient clinical data for legacy devices and also innovative products. Guidance on a methodology is lacking in a general sense and some framework should be provided by product class and device type. MDR introduced coding for medical devices. MDA/MDN codes have been introduced to reflect design and intended use of a device, these codes have been arranged based on device complexity with active implantable devices highest on the list. This research shall explore the difficulties encountered by manufacturers but also gather opinions on how these issues could be resolved. MDA/MDN codes could be used by regulators to provide guidance on clinical evidence based on device technology and complexity.

This research will cover areas that have not been explored previously.

The aim of this study is to identify specific barriers to MDR certification for manufacturers of legacy, intra-articular hyaluronic acid medical devices and evaluate the impact to patient quality of life in the event manufacturers cannot meet the new requirements.

The objectives of this study are as follows:

1. Examine key MDR 2017/745 compliance challenges for legacy devices, in particular, the impact of MDR clinical evidence requirements.

2. Compare current EU MDR 2017/745 framework versus US medical device regulatory framework and pharmaceutical product requirements with respect to clinical data.

3. Discover potential patient impact in the event of market shortage for implantable, intra-articular medical devices.

4. Propose possible routes forward for industry and regulators to ensure continuity of supply of implantable, intra-articular medical devices.

Information shall be collected in the form of questionnaires/ surveys and interviews with experts. A questionnaire will be developed using SurveyMonkey and issued to colleagues and disseminated via LinkedIn. Prior to finalizing the questionnaire, a pilot questionnaire will be sent to three colleagues for feedback. The data collected will be qualitative and quantitative in nature and analysed using thematic analysis and statistics.

The surveys will be targeted at Quality and Regulatory Affairs professionals within the medical device industry to gather information on how MDR has impacted businesses specifically in the area of clinical evaluation. Information will be predominantly gathered for legacy products but innovative products will be considered also as it was highlighted through literature review that there is a lack of understanding of required clinical evidence for these devices also. It is of interest to confirm this point as a lack of available legacy and innovative products has an even more significant patient impact than a lack of legacy devices only.

Review of MDCG guidelines along with the quantitative study by Kearney & McDermott (2023), shows that a key struggle for manufacturers is determining the amount of data needed to demonstrate sufficient clinical evidence. The survey will contain questions aimed to determine whether the clinical evidence requirements have resulted in significant investment for manufacturers and if there has been an impact to the on-market products such as reduction in indications and also gather opinions on how best for regulators to proceed.

Brand specific studies have been recommended by Migliore et. al., (2016). This is an interesting topic that could be extended to claiming equivalence. The idea of clinical studies based on equivalent products could give manufacturers an opportunity to collect data in a more collaborative manner.

Questions will be included in the surveys to determine the clinical data currently held by manufacturers. The aim is to receive one hundred responses.

A comparison of current EU MDR 2017/745 framework versus US medical device regulatory framework and pharmaceutical product requirements with respect to clinical data is aimed at identifying recommendations for management of legacy devices from a regulatory perspective.

Literature highlights the importance of HA injections for OA management (Pavone et. al., (2021), and Billesberger et. al., (2020)) and Rosen et. al., (2020) confirms cost-effectiveness of high molecular weight hyaluronic acid in treating patients suffering mild to moderate OA. This indicates the product is a valuable treatment option for patients in terms of efficacy and cost. Semi-structured, recorded interviews shall be conducted with subject matter experts from varying disciplines such as Clinicians, Pharmacists and Marketing personnel to understand the impact a market shortage would have on patients. It is planned to gather this information from colleagues in the Medical and Marketing areas. It is planned to interview five Clinicians/ Pharmacists and five Marketing experts.

In accordance with Economic and Social Research Council, (ESRC) UK – Guidelines, the following points will be of paramount importance:

- Research shall be collected and reviewed in a manner that ensures quality and integrity.
- All participants will be fully informed of the scope, purpose, recording and compilation of findings.
- All participants will be fully informed of the level of participation needed from them.
- All information provided by participants shall be confidential and anonymous.
- Participants are involved voluntarily.
- Harm to participants shall be avoided.

- The research must be independent and free from conflicts of interest.

Section 4 Summary and Timetable

Literature Review/ Secondary Research has concluded the following:

There are multiple studies/ reviews available summarizing the differences between MDD 93/42/EEC and MDR 2017/745. It is transparent that MDR requirements related to PMS, Vigilance, PMCF, registration of economic operators and market surveillance are applicable to legacy devices.

Although MDCG guidance documents provide guidance on claiming equivalence, relevant MDR GSPRs and a framework for preparing clinical evaluation there is a distinct lack of literature available to allow manufacturers to gather sufficient clinical evidence as required by the MDR. Literature review suggests that this problem is not limited to legacy intra-articular hyaluronic acid medical devices but is encountered by all medical device manufacturers planning to CE mark devices under MDR.

Information gathered to date indicates that EU MDR regulation has become a barrier to placing medical devices on market. Primary research is aimed at exploring this regulatory burden further and also the impact of possible medical device shortages in the European market. Primary research shall also assess if there are possible solutions to this problem that will benefit both industry and patients while ensuring products placed on the market are both safe and effective.

Activities will be carried out in accordance with the schedule below.

Schedule of activities

No.	Start Date	End Date	Task	Nov-23	Dec-23	Jan-24	Feb-24	Mar-24	Apr-24	May-24
1	01/11/2023	22/12/2023	Refine Research Objectives							
2	01/11/2023	22/12/2023	Literature Search							
3	01/01/2024	26/01/2024	Methodology							
4	01/01/2024	26/01/2024	Research Design							
5	26/01/2024	29/03/2024	Collecting primary data							
6	01/03/2024	30/04/2024	Data analysis/ interpretation							
7	30/04/2024	31/05/2024	Discussion							
8	30/04/2024	31/05/2024	Final Write Up							

References:

Medical Device Co-ordination Group (2020), *MDCG 2020-5 Clinical Evaluation – Equivalence - A guide for manufacturers and notified bodies April 2020* Available at: https://health.ec.europa.eu/system/files/2020-09/md_mdcg_2020_5_guidance_clinical_evaluation_equivalence_en_0.pdf

Medical Device Co-ordination Group (2020), *MDCG 2020-6 Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC A guide for manufacturers and notified bodies April 2020* Available at: https://ec.europa.eu/docsroom/documents/40904?locale=de

Medical Device Co-ordination Group (2021), *MDCG 2021-25 Regulation (EU) 2017/745 - application of MDR requirements to 'legacy devices' and to devices placed on the market prior to 26 May 2021 in accordance with Directives 90/385/EEC or 93/42/EEC October 2021* Available at: https://health.ec.europa.eu/system/files/2021-10/md_mdcg_2021_25_en_0.pdf

Medical Device Co-ordination Group (2021), *MDCG 2021-6 Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation April 2021* Available at: https://health.ec.europa.eu/system/files/2021-04/mdcg_2021-6_en_0.pdf

Clemens, N (2018), The European Medical Device Regulation 2017/745/EU: Changes and Impact on Stakeholder *Journal of Clinical Research best practices, Vol. 14, No. 9* Available at: https://www.researchgate.net/publication/327337806_The_European_Medical_Device_Regulation_2017745EU_Changes_and_Impact_on_Stakeholders

Smirthwaite. A (2021), BSI White Paper, *Clinical evaluation under EU MDR* Available at: https://www.bsigroup.com/globalassets/localfiles/en-gb/medical-devices/whitepapers/clinical-evaluation-white-paper/clinical-evaluation-under-eu-mdr.pdf

Kearney, B, McDermott, O (2023), Therapeutic Innovation & Regulatory Science, *The Challenges for Manufacturers of the Increased Clinical Evaluation in the European Medical Device Regulations: A Quantitative Study* Available at: https://pubmed.ncbi.nlm.nih.gov/37198369/

Behan, R, Watson, M, Pandit, A (2020) Molecular Medicine Ireland, Dublin, Ireland, CÚRAM – Centre for Research in Medical Devices, Galway, Ireland, *New EU medical device regulations: Impact on the MedTech sector* Available at: https://www.researchgate.net/publication/324963773_New_Eu_medical_device_regulations_Impact_on_the_medtech_sector

Maresova, P, Hajek,L, Krejcar, O, Storek, M, Kuca, K (2020) MDPI Administrative Science, *New Regulations on Medical Devices in Europe: Are They an Opportunity for Growth?* Available at: https://www.researchgate.net/publication/350459225_New_Regulations_on_Medical_Devices_in_Europe_Are_They_an_Opportunity_for_Growth

Rosen, J, Niazi, F, Dysart, S (2020), Advanced Therapy *Cost-Effectiveness of Treating Early to Moderate Stage Knee Osteoarthritis with Intra-articular Hyaluronic Acid Compared to Conservative Interventions* Available at: https://pubmed.ncbi.nlm.nih.gov/31735982/

Migliore, A, Bizzi, E, De Lucia, O, Delle Sedie, A, Bentivegna ,M, Mahmoud, A, Foti, C (2016) Libertas Academica *Differences among Branded Hyaluronic Acids in Italy, Part 1: Data from In Vitro and Animal Studies and Instructions for Use* Available at: https://pubmed.ncbi.nlm.nih.gov/27257398/

Pavone,V, Vescio,A, Turchetta,M, Chiara Giardina,S. Culmone, A, Testa, G (2021)Section of Orthopaedics, Department of General Surgery and Medical Surgical Specialties, A.O.U. Policlinico Rodolico – San Marco, University of Catania, Catania, Italy *Injection-Based Management of Osteoarthritis of the Knee: A Systematic Review of Guidelines* Available at: *https://pubmed.ncbi.nlm.nih.gov/33959026/*

Billesberger, L, Fisher,K. Qadri,Y, Boortz-Marx, R (2020) Hindawi Pain Research and Management Volume 2020, Article ID 3873098, *Procedural Treatments for Knee Osteoarthritis: A Review of Current Injectable Therapies* Available at: *https://pubmed.ncbi.nlm.nih.gov/32148599/*

Ethics Application & Declaration Form

DISSERTATION TITLE: The regulatory burden of Regulation 2017/745 placed on manufacturers of legacy devices and the potential impact of market shortages as manufacturers strive to comply.

RESEARCHER'S NAME: Kate Brennan

PROGRAMME OF STUDY: Master of Science in Medical Device Technology & Business

SUPERVISOR'S NAME: Gillian McMahon

DECLARATION:
The information in this application form is accurate to the best of my knowledge. I undertake to abide by the principles outlined by Innopharma/Griffith College ethics policy in my research dissertation. I confirm that I have completed a full ethics assessment for my research dissertation as per the college guidelines. I will not begin my primary research until such approval from my supervisor and/or ethics Committee has been obtained.
I pledge to carry out my research according to the Innopharma/Griffith College academic integrity standards. Any results presented in my dissertation will be from my own, original research, I will reference and/or acknowledge any material or sources used in its preparation and I will not plagiarise the work of anyone else.

For Student:
STUDENT SIGNATURE: Kate Brennan

DATE: 16/01/24

The research contained within this research dissertation proposal has been approved.

For Supervisor:
Ethics Committee Approval Required: Yes [ ] No [X]

SUPERVISOR SIGNATURE: Gillian McMahon

DATE: 16/01/24

For Ethics Committee (if required):
Ethics Committee Approval Given: Yes [ ] No [ ]

ETHICS COMMITTEE MEMBER SIGNATURE:

DATE:

NOTE: Supervisors are responsible for ensuring their students fill in this form correctly and that all ethical areas have been considered.

SECTION 1: DESCRIPTION OF RESEARCH STUDY

1.1 Purpose and objectives of research

To identify, define and describe the regulatory burden of Regulation 2017/745 placed on manufacturers of legacy implantable, intra-articular medical devices for treatment of Osteoarthritis and the potential impact of market shortages as manufacturers strive to comply.

The aim of this study is to identify specific barriers to MDR (Medical Device Regulation 2017/745) certification for manufacturers of the above-mentioned devices and evaluate the impact on patient quality of life in the event manufacturers cannot meet the new requirements.

The objectives of this study are as follows:

1. *Examine key MDR 2017/ 745 compliance challenges for legacy devices, in particular, the impact of MDR clinical evidence requirements.*
2. *Compare current EU MDR 2017/745 framework versus US medical device regulatory framework and pharmaceutical product requirements with respect to clinical data.*
3. *Discover potential impact on patients in the event of market shortage for implantable, intra-articular medical devices.*
4. *Propose possible routes forward for industry and regulators to ensure continuity of supply of implantable, intra-articular medical devices.*

1.2 Research methodology: *Information shall be collected in the form of questionnaires/ surveys and interviews with experts. A questionnaire will be developed, issued to colleagues and also disseminated via LinkedIn. Prior to finalizing the questionnaire, a pilot questionnaire will be sent to three colleagues for feedback. The data collected will be qualitative and quantitative in nature and analysed using thematic analysis and statistics.*

The surveys will be targeted at Quality and Regulatory Affairs professionals within the medical device industry to gather information on how MDR has impacted businesses specifically in the area of clinical evaluation. Information will be predominantly gathered for legacy products but innovative products will be considered also as it was highlighted through literature review that there is a lack of understanding of required clinical evidence for these devices also.

Semi-structured, recorded interviews shall be conducted with subject matter experts from varying disciplines such as Clinicians, Pharmacists and Marketing personnel to understand the impact a market shortage would have on patients. It is planned to gather this information from colleagues in the Medical and Marketing areas. It is planned to interview five Clinicians/ Pharmacists and five Marketing experts.

SECTION 2: POSSIBLE ETHICAL ISSUES

Answer 'yes' or 'no' to the following questions.

SUBJECT MATTER

Does the research proposal involve:

Research into specific company activities that would be deemed sensitive or confidential	Yes **No**
Research into politically and/or racially/ethnically and/or commercially sensitive areas	Yes **No**
Sensitive, personal, professional or corporate issues	Yes **No**

RESEARCH PROCEDURES

Does the research proposal involve:

Research that might damage the reputation of companies or participants	Yes **No**
Research that may negatively affect the reputation of Griffith College/Innopharma	Yes **No**
Use of personal records without consent	Yes **No**
Use of company data without consent	Yes **No**
The offer of any inducements to participate	Yes **No**
Audio or visual recording without consent	Yes **No**
Using a language other than English	Yes **No**

PARTICIPANTS
Does the research proposal involve:
People who are not competent and/or fluent in English — Yes **No**
Does your research group include any of the following vulnerable groups — Yes **No**
(Adults with psychological impairments; Adults with learning difficulties; Adults under the protection/control /influence of others (e.g. in care/prison); Relatives of ill people (e.g. parents of sick children); Hospital or GP participants recruited in a medical facility; persons under the age of 18)

If you have answered NO to ALL questions, please go straight to Section 4.

If you have answered YES to ANY question in SECTION 2, you must fill in SECTION 3.

SECTION 3: STEPS TAKEN TO AVOID ETHICAL ISSUES

[Only fill in this section if you answered YES to ANY of the questions in Section 3. For example, if you answered yes to including participants who are not fluent in English, you might put forward a plan that offers your survey in two languages to take this into account. Another example could be a study where the researcher wants to include information about the care received by children with a long-term condition but it would not be ethical to approach the children directly but it might be acceptable to instead ask parents questions about their child's care. If these plans are acceptable to your supervisor, you may not need to apply for ethical approval from the Ethics Committee].

3.1. If your ethics relates to ***Subject Matter***, outline your action plan to work around any sensitive issues.
3.2. If your ethics relates to ***Research Procedures***, outline your action plan to deal with possible ethical issues in your research procedures.
3.3. If your ethics relates to ***Participants***, outline how you will protect vulnerable persons or those that do not have English as their first language.

SECTION 4: ABOUT YOUR PARTICIPANTS

4.1. Outline your participant profile and why you have chosen them for this study
The surveys will be targeted at Quality and Regulatory Affairs professionals within the medical device industry to gather information on how MDR has impacted businesses specifically in the area of clinical evaluation.
Semi-structured, recorded interviews shall be conducted with subject matter experts from varying disciplines such as Clinicians, Pharmacists and Marketing personnel to understand the impact a market shortage would have on patients. It is planned to gather this information from colleagues in the Medical and Marketing areas.

4.2 How do you plan to gain access to/contact/approach your participant(s).

Surveys will be conducted in the form of questionnaires disseminated by email or social media via LinkedIn.
Clinicians, Pharmacists and Marketing colleagues will be approached by phone or email to explain the purpose of the study and provide the opportunity to opt in or out of the study.

SECTION 5: INFORMATION, CONSENT AND CONFIDENTIALITY

5.1 **Participant Information Letter (PIL) for participants**

[You must submit an information letter for participants with this application, as part of your appendices document. For online surveys, it is sufficient to include a paragraph summarising and explaining the purpose of the research at the beginning of the survey. In all other research e.g. interviews, phonecalls, a PIL should be provided to each participant before they are asked for their consent to take part. A template PIL is available in Moodle].

Please confirm below that your information letter covers:
Description of the research topic and method — **Yes** No

Details of what participation will involve **Yes** No
Rights to anonymity **Yes** No
Confidentiality **Yes** No
Rights to withdraw from the research **Yes** No
The contact details of the researcher and supervisor (if necessary) **Yes** No

5.2 **Informed Consent Form (ICF) for participants**

[Informed consent is required for most research. For online surveys, it is sufficient to get the participant to tick two boxes at the beginning of the survey – one to state they understand the research and one to give consent. In all other research e.g. interviews, phonecalls, a signed consent form is required. If the data is gathered online e.g. zoom, a signed consent form can be scanned and sent to the researcher. A template ICF is available in Moodle. The signed ICFs, along with the surveys, audio files or interview notes etc. must be stored in the primary data folder on moodle and can be accessed by Innopharma staff for the purposes of verifying the authenticity of the research carried out and the data collected].

Please indicate below if your research requires a signed consent form by selecting the relevant option only:

Yes: my research requires signed consent and I have attached an ICF in the appendices of my application.

SECTION 6: STORAGE OF DATA

[Please ensure that you are abiding by GDPR and the national Data protection laws https://www.hrb.ie/funding/gdpr-guidance-for-researchers/gdpr-and-health-research/).

The student is responsible for storage of data and this will be handed over to the college in an electronic format as part of the thesis submission i.e. primary data and completed ICFs where applicable will be added to the primary data folder on moodle. The rationale is to keep data ***as long as it is still useful*** *and there is an intention to use it further* ***for research*** *so if this is not the case then this can be stipulated here and a shorter retention period given.]*

6.1. How will you store the research data and for how long? How will you manage data protection issues?

The data will be retained for two years after completion of the course.

SECTION 7: NON-DISCLOSURE AGREEMENT & STUDENT CONSENT

7.1 **Non-Disclosure Agreement (NDA)**
Will the final dissertation contain any information pertaining to any source what would warrant the use of a Non-Disclosure Agreement (NDA) e.g. industry-based research?

Yes **No**

7.2 **Student consent**
If a Non-Disclosure Agreement (NDA) is not required, does the Student consent to allow their completed dissertation to be held/published by Innopharma/Griffith College?

Yes No

SECTION 8: RECORDING AND RETENTION OF DISSERTATION VIVA

8.1 **Viva Recording**
The Dissertation viva will be recorded. This recording may be used to facilitate assessment by Innopharma staff, a third reader if necessary and/or if requested by the external examiner for the Programme. The recording will be held in line with current GDPR guidelines and will not be made publicly available.

SECTION 9: DOCUMENT CHECKLIST

NOTE: Applicants must attach the following documents in electronic format to the appendix.

Which documents are added to the appendix? Please tick N/A if not applicable:

9.1 Participant Information Letter (PIL) for participant	**Yes** N/A
9.2 Informed Consent Form (ICF) for participant	**Yes** N/A
9.3 Questions/survey for interviewees/focus groups etc *(can be in draft form)*	**Yes** N/A
9.4 Any other documents e.g. Non-Disclosure Agreement	Yes **N/A**

I confirm that this application is complete and all required documents are included in the appendix.

For Student:
STUDENT SIGNATURE: Kate Brennan

DATE: 16/01/24

SECTION 10: APPENDIX

Participant Information Letter

TITLE OF THE STUDY

The regulatory burden of Regulation 2017/745 placed on manufacturers of legacy devices and the potential impact of market shortages as manufacturers strive to comply.

I would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Ask questions if anything you read is not clear or if you would like more information. Take time to decide whether or not to take part.

WHO I AM AND WHAT THIS STUDY IS ABOUT

The purpose of this study is to identify, define and describe the regulatory burden of Regulation 2017/745 placed on manufacturers of legacy implantable, intra-articular medical devices for treatment of Osteoarthritis and the potential impact of market shortages as manufacturers strive to comply. This research is part of my dissertation in my course, Master of Science in Medical Device Technology & Business. I expect to learn how the challenges of MDR 2017/745 have impacted the medical device industry and the potential knock-on effect for patients in the event of market shortages.

WHAT WOULD TAKING PART INVOLVE?

Taking part will require a maximum of 30 minutes of your time in the form of a recorded interview. I would like to use the time with you to learn your perspectives in your area of expertise. The interview will be recorded for transcribing later.

WHY HAVE YOU BEEN INVITED TO TAKE PART?

I have selected you for participation as you are subject matter expert in this field and your perspectives will be valuable.

DO YOU HAVE TO TAKE PART?

No. Participation is completely **voluntary** and you have the right to refuse participation, refuse any question and withdraw at any time without consequence.

Should you wish to withdraw at any time prior to interview please contact kateheeney8760@gmail.com

WHAT ARE THE POSSIBLE RISKS AND BENEFITS OF TAKING PART?

There are no risks of harm to the participant as the information provided by them will be anonymized. The data will remain confidential and will only be used for the purposes of this research.

WILL TAKING PART BE CONFIDENTIAL?

Yes. No identifying information shall be published in the dissertation. Identifying information can only be accessed by my supervisor and examining academic staff for the purpose of verifying the data as true and credible.

The researcher may breach confidentiality if in belief that there is a serious risk of harm or danger to either the participant or another individual (e.g. physical, emotional or sexual abuse, concerns for child protection, rape, self-harm, suicidal intent or criminal activity) or if a serious crime has been committed. Non-anonymised data in the form of signed consent forms and audio recordings will be collected and retained as part of the research process.

HOW WILL INFORMATION YOU PROVIDE BE STORED AND PROTECTED?

Signed consent forms and original audio recordings will be retained in electronic format on the Griffith College IT system until after my degree has been conferred. A transcript of interviews in which all identifying information has been removed will be retained for a further two years after this. Under freedom of information legalisation you are entitled to access the information you have provided at any time.

WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY?

This research shall be submitted as part of the dissertation only. Please note that all dissertation research projects and their content will be made accessible in the college library and could potentially be made available in online e-journals or repository.

WHO SHOULD YOU CONTACT FOR FURTHER INFORMATION?

Name Kate Brennan

Degree Programme: Master of Science in Medical Device Technology & Business

College Details: Griffith College Dublin

Contact number 0879266849

Contact mail kateheeney8760@gmail.com

THANK YOU

Consent to take part in research

Research Title - The regulatory burden of Regulation 2017/745 placed on manufacturers of legacy devices and the potential impact of market shortages as manufacturers strive to comply.

The researcher retains one copy signed by both themselves and the participant. The participant should also receive a copy of consent form as a record of what they have signed up to.

- I [*insert participant name*] voluntarily agree to participate in this research study
- I understand that even if I agree to participate now, I can withdraw at any time or refuse to answer any question without any consequences of any kind
- I understand that I can withdraw permission to use data from my interview within two weeks after the interview, in which case the material will be deleted.
- I have had the purpose and nature of the study explained to me in writing and I have had the opportunity to ask questions about the study
- I understand that participation involves an interview that will be recorded for the purpose of transcription.
- I understand that I will not benefit directly from participating in this research.
- I understand that all information I provide for this study will be treated confidentially.
- I understand that in any report on the results of this research my identity will remain anonymous. This will be done by changing my name and disguising any details of my interview which may reveal my identity or the identity of people I speak about.
- I agree to my interview being audio-recorded.
- I understand that disguised extracts from my interview may be quoted in the students' dissertation.
- I understand that if I inform the researcher that myself or someone else is at risk of harm, they may have to report this to the relevant authorities - they will discuss this with me first but may be required to report with or without my permission.
- I understand that signed consent forms and original audio recordings will be retained for two years after the course has been completed.
- I understand that a transcript of my interview in which all identifying information has been removed will be retained for two years from the date of the exam board.

- I understand that under freedom of information legalisation I am entitled to access the information I have provided at any time while it is in storage as specified above.
- I understand that I am free to contact any of the people involved in the research to seek further clarification and information.

Researcher Details

Name Kate Brennan

Degree Programme: Master of Science in Medical Device Technology & Business

College Details: Griffith College Dublin

Contact number 0879266849

Contact mail kateheeney8760@gmail.com

Signature of participant

[Full Name – Printed]

Signature of research participant

--- -------------------- Date

Signature of researcher

I believe the participant is giving informed consent to participate in this study

-- ---------------------- Date

Signature of researcher

Questionnaire

I would like to invite you to take part in a research study.

This research is part of my dissertation. My course of study is Master of Science in Medical Device Technology & Business. I expect to learn how the challenges of a new EU regulation, referred to as MDR 2017/745, has impacted the medical device industry and the potential knock-on effect for patients in the event of market shortages.

This survey is targeted at Quality Assurance and Regulatory Affairs professionals within the medical device industry to gather information on how MDR has impacted businesses specifically in the area of clinical evaluation. Information will be predominantly gathered for legacy products but innovative products will also be considered.

TITLE OF THE STUDY

The regulatory burden of Regulation 2017/745 placed on manufacturers of legacy devices and the potential impact of market shortages as manufacturers strive to comply.

AIM OF THIS STUDY

The aim of this study is to identify specific barriers to MDR (Medical Device Regulation 2017/745) certification for manufacturers of the above-mentioned devices and evaluate the impact on patient quality of life in the event manufacturers cannot meet the new requirements.

I am conducting this study to determine the following:

1. Examine key MDR 2017/ 745 compliance challenges for legacy devices, in particular, the impact of MDR clinical evidence requirements.

2. Propose possible routes forward for industry and regulators to ensure continuity of supply of implantable, intra-articular medical devices.

I would like to thank you in advance for your valuable contribution to my studies.

Please take note of the following prior to completing the questionnaire:

- You have the right to refuse participation
- All data will be anonymised in accordance with GDPR legislation
- The data collected will be retained for two years after completion of the course.

Please tick the appropriate box in each question below prior to completion of the questionnaire.

I, the participant, understand the research and the aim of the research ***YES ☐ NO☐***

I, the participant, give consent for the information provided by me to be used by the researcher

YES ☐ NO☐

QUESTIONNAIRE

General

Please indicate your age range (tick appropriate box)	
21-25 years	
25-35 years	
35-45 years	
45-55 years	
55+ years	

Please indicate your years of experience in the medical device field (tick appropriate box)	
0 - 5 years	
5 - 10 years	
10 - 15 years	
15 - 20 years	
20+ years	

Please indicate your area of expertise	
Quality Assurance	
Regulatory Affairs	
Medical/ Clinical Affairs	
Other	

Please indicate the country in which you work
____

General Questions related to MDR 2017/745

1. ***Please indicate the classification of your medical devices under MDR 2017/745 (tick multiple boxes if required)***

Class	*Tick to indicate YES*
I	
IIa	
IIb	
III	

2. ***Please indicate the device type (one selection)***

Type	*Tick to indicate YES*
Legacy	
Novel/ Innovative	
Both	

3. ***Please indicate if your device has been reclassified according to MDR 2017/745 (tick appropriate box)***

YES ☐ NO☐

4. ***Please indicate other territories in which your devices are sold (tick boxes as appropriate)***

United States	
Canada	
Japan	
Brazil	
Australia	
Other	

5. ***To what extent do you agree with the following:***

	Strongly Disagree	*Disagree*	*Neutral*	*Agree*	*Strongly Agree*
Notified Body scrutiny procedure for higher risk devices is clear to me					
Requirements related to registration of Economic Operators are clear to me					
I understand EUDAMED functionality and registration requirements					
Increased scrutiny of the supply chain has been a challenge for my organisation					
MDR 2017/745 Technical Documentation requirements are clear to me					
Unique device identifier requirements are clear for each device class					
Labelling Requirements & relevant GSPRs are clear for me					
Post Market Surveillance requirements are clear for me					
Vigilance Reporting Requirements are clear for me					

6. ***To what extent do you agree with the following:***

	Strongly Agree	*Disagree*	*Neutral*	*Agree*	*Strongly Agree*
Preparation of Technical Documentation according to MD 2017/745 has been costly for my organisation					
Preparation of Technical Documentation according to MD 2017/745 has been labour intensive for my organisation					
Additional resources have been employed by my organisation to meet MDR 2017/745 requirements					
There is sufficient support available from regulatory bodies to provide guidance for manufacturers to meet MDR 2017/745 requirements (Notified Bodies and Health Authorities)					
The transition period for compliance with MDR 2017/745 is sufficient					

Clinical Evidence Questions

1. ***Under MDD 93/42/EEC, did your organisation claim equivalence to another device in order to meet clinical evidence requirements (please tick appropriate box)***

YES ☐ NO☐ N/A ☐

2. ***Please indicate the sources of Clinical Evaluation Data used by your organisation to comply with MDR 2017/745 (tick boxes as appropriate)***

Literature Search	
Clinical Investigation	
Post Market Clinical Follow Up Studies	
Post Market Surveillance Data	
Other	

3. ***With respect to Clinical Evidence required for your device(s) please indicate Yes or No for the following statements:***

	Yes	*No*	*N/A*
Guidance documents MDCG 2020-5 & MDCG 2020-6 provide adequate guidance on clinical evaluation requirements from MedDev 2.7/1 rev 4 and Article 61 and Annex XIV Part A of the EU MDR			
I understand methodologies that should be used to collect sufficient clinical evidence for my device(s)			
Clinical evidence gathered for my devices under MDD 93/42/EEC is sufficient to support the intended purpose and associated clinical benefits of the device(s) as well as the conditions of use and specific contraindications			
Clinical evidence gathered for my devices under MDD 93/42/EEC is sufficient to support all indications statements			
Clinical evidence gathered for my devices under MDD 93/42/EEC is sufficient for all potential patient populations			
Clinical evidence gathered for my devices under MDD 93/42/EEC is sufficient to support all device variants and combinations			
Clinical evidence gathered for my devices under MDD 93/42/EEC is sufficient to support the device lifetime in use			

4. ***In order to comply with MDR 2017/745 requirements regarding clinical evidence has your organisation revised the following: (tick as appropriate)***

	Yes	*No*
Device Intended Purpose		
Device Indications		
Device Contraindications		
Residual Risks associated with use of the device		

5. ***If yes selected for any item listed in question 4 above please indicate if the changes are expected to have a negative patient impact i.e., is it likely that there will be a restriction in patients accessing the device.***

YES ☐ NO☐ N/A ☐

6. ***If yes selected for any item listed in question 4 above please indicate if the changes are expected to impact registrations in markets outside the European market.***

YES ☐ NO☐ N/A ☐

7. ***If yes selected for any item listed in question 4 above please indicate if the changes are expected to negatively affect your organisation from a sales perspective.***

YES ☐ NO☐ N/A ☐

Outsourcing of Activities/ Business Impacts

1. ***Please indicate if your company has outsourced any of the following activities to fulfil MDR 2017/745 requirements:***

	Yes	*No*	*Don't Know*
Technical Documentation Compilation			
Periodic Safety Update Report Compilation			
PRRC Role (Person Responsible for Regulatory Compliance)			
Clinical Evaluation Report Compilation			
Post Market Clinical Follow Up Report Compilation			
Post Market Surveillance Activities			
Labelling Activity			
Internal Audits/ Self Inspection			

Interview Questions

General

Please indicate your age range (tick appropriate box)	
21-25 years	
25-35 years	
35-45 years	
45-55 years	
55+ years	

Please indicate your years of experience in your area of expertise (tick appropriate box)	
0 - 5 years	
5 - 10 years	
10 - 15 years	
15 - 20 years	
20+ years	

Please indicate your area of expertise	
Medicine/ Clinician	
Sales & Marketing	
Medical/ Clinical Affairs	
Pharmacy	
Other	

General Questions relating to Osteoarthritis

1. In your experience what is the age profile of most patients suffering with mild/ moderate Osteoarthritis.
2. Can you please tell me the most prevalent joint with patients suffer?
3. Can you please describe the most common symptoms patients present with?
4. Is reduced physical function a common complaint amongst the OA patients?
5. In general, how does OA impact a patient QoL?

Interview Questions

Specific Questions relating to Intra-articular medical devices

6. Are you experienced or knowledgeable in administration of intra-articular products such as Euflexxa, Suplasyn or Synvisc?
7. Do you agree these products play a key role for sufferers of mild/ moderate OA?
8. How would you describe the performance of intra-articular HA in alleviating patient discomfort?
9. How would you describe your confidence in the safety of intra-articular HA products?
10. Would you agree that intra-articular HA products have fewer side effects compared to oral NSAIDs?
11. What are the most common side effects experienced by patients undergoing treatments with intra-articular HA products?
12. Do you feel that the improvements in QoL outweigh any potential risks of side effects associated with these products?
13. In your opinion, what is the safest, most cost effective and beneficial treat for OA patients?
14. Are you experienced or knowledgeable in administration of intra-articular Platelet Rich Plasma treatments?
15. Do you think an implant card is beneficial for this type of product?

Questions related to patient impact in the event of a market shortage

16. What impact would it have for patients in the event intra-articular HA products were in short supply in the market?
17. In the event of lack of supply, what would be the impact to existing users QoL?

Questionnaire

I would like to invite you to take part in a research study.

This research is part of my dissertation. My course of study is Master of Science in Medical Device Technology & Business. I expect to learn how the challenges of a new EU regulation, referred to as MDR 2017/745, has impacted the medical device industry and the potential knock-on effect for patients in the event of market shortages.

This survey is targeted at Quality Assurance and Regulatory Affairs professionals within the medical device industry to gather information on how MDR 2017/745 has impacted businesses specifically in the area of clinical evaluation. Information will be predominantly gathered for legacy products but innovative products will also be considered.

TITLE OF THE STUDY

The regulatory burden of Regulation MDR 2017/745 placed on manufacturers of legacy devices and the potential impact of market shortages as manufacturers strive to comply.

AIM OF THIS STUDY

The aim of this study is to identify specific barriers to MDR (Medical Device Regulation 2017/745) certification for manufacturers of legacy devices and evaluate the impact on patient quality of life in the event manufacturers cannot meet the new requirements.

I am conducting this study to determine the following:

1. Examine key MDR 2017/ 745 compliance challenges for legacy devices, in particular, the impact of MDR clinical evidence requirements.

2. Propose possible routes forward for industry and regulators to ensure continuity of supply of implantable, intra-articular medical devices.

There are twenty questions in total.
I would like to thank you in advance for your valuable contribution to my studies.

Please take note of the following prior to completing the questionnaire:

- You have the right to refuse participation
- All data will be anonymised in accordance with GDPR legislation
- The data collected will be retained for two years after completion of the course.

* Required

1. *I, the participant, understand the research and the aim of the research* *

- ◯ Yes
- ◯ No

2. *I, the participant, give consent for the information provided by me to be used by the researcher*
*

◯ Yes

◯ No

General

3. **Please indicate your age range (tick appropriate box)** *

- ◯ 21-25 years
- ◯ 25-35 years
- ◯ 35-45 years
- ◯ 45-55 years
- ◯ 55+ years

4. **Please indicate your years of experience in the medical device field (tick appropriate box)** *

- ◯ 0 - 5 years
- ◯ 5 - 10 years
- ◯ 10 - 15 years
- ◯ 15 - 20 years
- ◯ 20+ years

5. **Please indicate your area of expertise** *

- ◯ Quality Assurance
- ◯ Regulatory Affairs
- ◯ Medical/ Clinical Affairs
- ◯ Other

6. **Please indicate the country in which you work** *

General Questions related to MDR 2017/745

7. ***Please indicate the classification of your medical devices under MDR 2017/745 (tick multiple boxes if required)*** *

- [ ] I
- [ ] IIa
- [ ] IIb
- [ ] III

8. ***Please indicate the device type (one selection)*** *

- ( ) Legacy
- ( ) Novel/ Innovative
- ( ) Both

9. ***Please indicate if your device has been reclassified according to MDR 2017/745 (tick as appropriate)*** *

- ( ) Yes
- ( ) No

10. ***Please indicate other territories in which your devices are sold (tick boxes as appropriate)*** *

- [ ] United States
- [ ] Canada
- [ ] Japan
- [ ] Brazil
- [ ] Australia
- [ ] Other

11. ***To what extent do you agree with the following:*** *

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Notified Body scrutiny procedure for higher risk devices is clear to me	○	○	○	○	○
Requirements related to registration of Economic Operators are clear to me	○	○	○	○	○
I understand EUDAMED functionality and registration requirements	○	○	○	○	○
Increased scrutiny of the supply chain has been a challenge for my organisation	○	○	○	○	○
MDR 2017/745 Technical Documentation requirements are clear to me	○	○	○	○	○
Unique device identifier requirements are clear for each device class	○	○	○	○	○
Labelling Requirements & relevant GSPRs are clear for me	○	○	○	○	○
Post Market Surveillance requirements are clear for me	○	○	○	○	○
Vigilance Reporting Requirements are clear for me	○	○	○	○	○

12. ***To what extent do you agree with the following:*** *

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Preparation of Technical Documentation according to MDR 2017/745 has been costly for my organisation	◯	◯	◯	◯	◯
Preparation of Technical Documentation according to MDR 2017/745 has been labour intensive for my organisation	◯	◯	◯	◯	◯
Additional resources have been employed by my organisation to meet MDR 2017/745 requirements	◯	◯	◯	◯	◯
There is sufficient support available from regulatory bodies to provide guidance for manufacturers to meet MDR 2017/745 requirements (Notified Bodies and Health Authorities)	◯	◯	◯	◯	◯
The transition period for compliance with MDR 2017/745 is sufficient	◯	◯	◯	◯	◯

Clinical Evidence Questions

13. ***Under MDD 93/42/EEC, did your organisation claim equivalence to another device in order to meet clinical evidence requirements (please tick as appropriate)***

- ◯ Yes
- ◯ No
- ◯ N/A

14. ***Please indicate the sources of Clinical Evaluation Data used by your organisation to comply with MDR 2017/745 (tick boxes as appropriate)***

- ☐ Literature Search
- ☐ Clinical Investigation
- ☐ Post Market Clinical Follow Up Studies
- ☐ Post Market Surveillance Data
- ☐ Other

15. ***With respect to Clinical Evidence required for your device(s) please indicate Yes or No for the following statements:***

	Yes	No	N/A
Guidance documents MDCG 2020-5 & MDCG 2020-6 provide adequate guidance on clinical evaluation requirements from MedDev 2.7/1 rev 4 and Article 61 and Annex XIV Part A of the EU MDR	◯	◯	◯
I understand methodologies that should be used to collect sufficient clinical evidence for my device(s)	◯	◯	◯
Clinical evidence gathered for my devices under MDD 93/42/EEC is sufficient to support the intended purpose and associated clinical benefits of the device(s) as well as the conditions of use and specific contraindications	◯	◯	◯
Clinical evidence gathered for my devices under MDD 93/42/EEC is sufficient to support all indications statements	◯	◯	◯
Clinical evidence gathered for my devices under MDD 93/42/EEC is sufficient for all potential patient populations	◯	◯	◯
Clinical evidence gathered for my devices under MDD 93/42/EEC is sufficient to support all device variants and combinations	◯	◯	◯
Clinical evidence gathered for my			

gathered for my devices under MDD 93/42/EEC is sufficient to support the device lifetime in use

16. ***[...]nply with MDR 2017/745 requirements regarding clinical evidence has [...]tion revised the following: (tick as appropriate)***

	Yes	No
Device Intended Purpose	◯	◯
Device Indications	◯	◯
Device Contraindications	◯	◯
Residual Risks associated with use of the device	◯	◯

17. ***If yes selected for any item listed in question 16 above please indicate if the changes are expected to have a negative patient impact i.e., is it likely that there will be a restriction in patients accessing the device.***

◯ Yes

◯ No

◯ N/A

18. ***If yes selected for any item listed in question 16 above please indicate if the changes are expected to impact registrations in markets outside the European market.***

◯ Yes

◯ No

◯ N/A

19. ***If yes selected for any item listed in question 16 above please indicate if the changes are expected to negatively affect your organisation from a sales perspective.***

◯ Yes

◯ No

◯ N/A

Outsourcing of Activities/ Business Impacts

20. ***Please indicate if your company has outsourced any of the following activities to fulfil MDR 2017/745 requirements:***

	Yes	No	Don't Know
Technical Documentation Compilation	◯	◯	◯
Periodic Safety Update Report Compilation	◯	◯	◯
PRRC Role (Person Responsible for Regulatory Compliance)	◯	◯	◯
Clinical Evaluation Report Compilation	◯	◯	◯
Post Market Clinical Follow Up Report Compilation	◯	◯	◯
Post Market Surveillance Activities	◯	◯	◯
Labelling Activity	◯	◯	◯
Internal Audits/ Self Inspection	◯	◯	◯

This content is neither created nor endorsed by Microsoft. The data you submit will be sent to the form owner.

Microsoft Forms

Consent to take part in research

Research Title - The regulatory burden of Regulation 2017/745 placed on manufacturers of legacy devices and the potential impact of market shortages as manufacturers strive to comply.

The researcher retains one copy signed by both themselves and the participant. The participant should also receive a copy of consent form as a record of what they have signed up to.

- I [ ] voluntarily agree to participate in this research study
- I understand that even if I agree to participate now, I can withdraw at any time or refuse to answer any question without any consequences of any kind
- I understand that I can withdraw permission to use data from my interview within two weeks after the interview, in which case the material will be deleted.
- I have had the purpose and nature of the study explained to me in writing and I have had the opportunity to ask questions about the study
- I understand that participation involves an interview that will be recorded for the purpose of transcription.
- I understand that I will not benefit directly from participating in this research.
- I understand that all information I provide for this study will be treated confidentially.
- I understand that in any report on the results of this research my identity will remain anonymous. This will be done by changing my name and disguising any details of my interview which may reveal my identity or the identity of people I speak about.
- I agree to my interview being audio-recorded.
- I understand that disguised extracts from my interview may be quoted in the students' dissertation.
- I understand that if I inform the researcher that myself or someone else is at risk of harm, they may have to report this to the relevant authorities - they will discuss this with me first but may be required to report with or without my permission.
- I understand that signed consent forms and original audio recordings will be retained for two years after the course has been completed.
- I understand that a transcript of my interview in which all identifying information has been removed will be retained for two years from the date of the exam board.

- I understand that under freedom of information legalisation I am entitled to access the information I have provided at any time while it is in storage as specified above.
- I understand that I am free to contact any of the people involved in the research to seek further clarification and information.

Researcher Details

Name Kate Brennan

Degree Programme: Master of Science in Medical Device Technology & Business

College Details: Griffith College Dublin

Contact number 0879266849

Contact mail kateheeney8760@gmail.com

Signature of participant

[ ]

Signature of research participant

Date

Signature of researcher

I believe the participant is giving informed consent to participate in this study

Date

Signature of researcher

Participant Information Letter

TITLE OF THE STUDY

The regulatory burden of Regulation 2017/745 placed on manufacturers of legacy devices and the potential impact of market shortages as manufacturers strive to comply.

I would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Ask questions if anything you read is not clear or if you would like more information. Take time to decide whether or not to take part.

WHO I AM AND WHAT THIS STUDY IS ABOUT

The purpose of this study is to identify, define and describe the regulatory burden of Regulation 2017/745 placed on manufacturers of legacy implantable, intra-articular medical devices for treatment of Osteoarthritis and the potential impact of market shortages as manufacturers strive to comply. This research is part of my dissertation in my course, Master of Science in Medical Device Technology & Business. I expect to learn how the challenges of MDR 2017/745 have impacted the medical device industry and the potential knock-on effect for patients in the event of market shortages.

WHAT WOULD TAKING PART INVOLVE?

Taking part will require a maximum of 30 minutes of your time in the form of a recorded interview. I would like to use the time with you to learn your perspectives in your area of expertise. The interview will be recorded for transcribing later.

WHY HAVE YOU BEEN INVITED TO TAKE PART?

I have selected you for participation as you are subject matter expert in this field and your perspectives will be valuable.

DO YOU HAVE TO TAKE PART?

No. Participation is completely **voluntary** and you have the right to refuse participation, refuse any question and withdraw at any time without consequence.

Should you wish to withdraw at any time prior to interview please contact
kateheeney8760@gmail.com

WHAT ARE THE POSSIBLE RISKS AND BENEFITS OF TAKING PART?

There are no risks of harm to the participant as the information provided by them will be anonymized. The data will remain confidential and will only be used for the purposes of this research.

WILL TAKING PART BE CONFIDENTIAL?

Yes. No identifying information shall be published in the dissertation. Identifying information can only be accessed by my supervisor and examining academic staff for the purpose of verifying the data as true and credible.

The researcher may breach confidentiality if in belief that there is a serious risk of harm or danger to either the participant or another individual (e.g. physical, emotional or sexual abuse, concerns for child protection, rape, self-harm, suicidal intent or criminal activity) or if a serious crime has been committed. Non-anonymised data in the form of signed consent forms and audio recordings will be collected and retained as part of the research process.

HOW WILL INFORMATION YOU PROVIDE BE STORED AND PROTECTED?

Signed consent forms and original audio recordings will be retained in electronic format on the Griffith College IT system until after my degree has been conferred. A transcript of interviews in which all identifying information has been removed will be retained for a further two years after this. Under freedom of information legalisation you are entitled to access the information you have provided at any time.

WHAT WILL HAPPEN TO THE RESULTS OF THE STUDY?

This research shall be submitted as part of the dissertation only. Please note that all dissertation research projects and their content will be made accessible in the college library and could potentially be made available in online e-journals or repository.

WHO SHOULD YOU CONTACT FOR FURTHER INFORMATION?

Name Kate Brennan

Degree Programme: Master of Science in Medical Device Technology & Business

College Details: Griffith College Dublin

Contact number 0879266849

Contact mail kateheeney8760@gmail.com

THANK YOU

Interview Questions

Interview Questions

General

Please indicate your age range (tick appropriate box)	
21-25 years	
25-35 years	
35-45 years	
45-55 years	
55+ years	

Please indicate your years of experience in your area of expertise (tick appropriate box)	
0 - 5 years	
5 - 10 years	
10 - 15 years	
15 - 20 years	
20+ years	

Please indicate your area of expertise	
Medicine/ Clinician	
Sales & Marketing	
Medical/ Clinical Affairs	
Pharmacy	
Other	

General Questions relating to Osteoarthritis

1. In your experience what is the age profile of most patients suffering with mild/ moderate Osteoarthritis.
2. Can you please tell me the most prevalent joint with patients suffer?
3. Can you please describe the most common symptoms patients present with?
4. Is reduced physical function a common complaint amongst the OA patients?
5. In general, how does OA impact a patient QoL?

Specific Questions relating to Intra-articular medical devices

6. Are you experienced or knowledgeable in administration of intra-articular products such as Euflexxa, Suplasyn or Synvisc?
7. Do you agree these products play a key role for sufferers of mild/ moderate OA?
8. How would you describe the performance of intra-articular HA in alleviating patient discomfort?
9. How would you describe your confidence in the safety of intra-articular HA products?
10. Would you agree that intra-articular HA products have fewer side effects compared to oral NSAIDs?
11. What are the most common side effects experienced by patients undergoing treatments with intra-articular HA products?
12. Do you feel that the improvements in QoL outweigh any potential risks of side effects associated with these products?
13. In your opinion, what is the safest, most cost effective and beneficial treat for OA patients?
14. Are you experienced or knowledgeable in administration of intra-articular Platelet Rich Plasma treatments?
15. Do you think an implant card is beneficial for this type of product?

Questions related to patient impact in the event of a market shortage

16. What impact would it have for patients in the event intra-articular HA products were in short supply in the market?
17. In the event of lack of supply, what would be the impact to existing users QoL?