A qualitative study exploring policy-amenable factors influencing medical device-related patient safety from a lifecycle perspective

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Kathleen Rose Harkin

BA, MB BCh BAO, DTM&H, MSc HTA&M, PGCert Stats

Centre for Health Policy and Management

School of Medicine

Trinity College Dublin

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Supervisors

Prof Steve Thomas (TCD)

Prof Jan Soresen (RCSI)

Declaration

I, Kathleen Harkin, declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work.

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Student No. 83002049

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Summary

The purpose of this research was to improve medical device safety by identifying the risks arising from the different stages in the life of a medical device and exploring policy options to address those risks.

This thesis examines factors influencing medical device safety from a lifecycle perspective, first by examining what is meant by the medical device lifecycle and lifecycle evaluation, and the influence that differences in meaning have had on medical device safety; and secondly, by examining how regulatory policy has affected device safety across its lifecycle.

It finds that, whilst many support the adoption of a lifecycle approach to the evaluation of medical devices, it was the adoption of a lifecycle approach by regulators that resulted in the lack of evidence regarding safety and efficacy of devices at market entry. This is due to the fact that the promise of evidence generation in the post-market stage is factored into pre-market decision-making, allowing devices with minimal supporting evidence onto the market based on the assumption that this evidence will become available when the device is in use.

The regulatory process for medical devices in the EEC was established to remove barriers to trade caused by the differing product safety requirements of its member states. It adopted a system requiring that manufacturers meet certain 'essential requirements' beyond which the member states could make no further demands. These essential requirements included adopting a quality system for all or part of the device's development process, and a risk management system to minimise the known or anticipated hazards associated with that type of device. To provide a means of proving and assessing compliance with these requirements, non-mandatory harmonised standards are provided, whose use confers a presumption of compliance. Compliance is assessed by reviewing the manufacturers' documentation on its quality and risk management systems, monitoring the application of these systems, and site inspections by independent notified bodies contracted by the manufacturers to perform the assessment. The data gathered in this process is legally protected by confidentiality clauses. The notified bodies do not approve medical devices, rather they verify that the documentation and the quality system is adequate. Whilst this does require 'clinical data', it does not require evidence of clinical effectiveness. Manufacturers present a declaration that they are compliant with the legal requirements and their notified body approves their affixing of the CE marking on their devices as proof of compliance. The CE marking does not mean that a device is safe or effective. Whilst the EU's revision of this regulatory process has introduced changes promising greater transparency of the clinical evidence

underpinning the CE marking, it does not fundamentally alter the regulatory approach, and the promised transparency has yet to be seen.

Furthermore, it finds that industry has been involved at multiple levels and in multiple ways in designing the rules by which it is regulated, demonstrating the capture of medical device regulation in the EU by industry. This must be kept in mind when the regulatory process is proclaimed to be rigorous and strict.

Therefore, there is a need to improve awareness of this problem, and to demand patient-centred regulation and better evidence. At the very least, policymakers must be made aware that the CE marking does not mean that devices are safe or effective and need to be reticent of making funding decisions on this basis. They should also demand a better regulatory system for implantable devices to ensure their safety and effectiveness through a centralised regulatory authority responsible for assessing the evidence and approving devices before they can be placed on the market. Demands should be placed on manufacturers to provide robust and reliable evidence of safety and efficacy before being allowed to market their devices, and certainly before they are purchased by healthcare providers. Healthcare systems should take responsibility for those devices, and their effects, that they implant into patients. They should gather, evaluate, and disseminate the necessary evidence to assess the safety and effectiveness of these devices so that patient outcomes can improved and clinical decision-making can be evidence-based.

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Abbreviations

Abbreviation	Term
AB (NAB)	Accreditation body (National accreditation body)
AHWP	Asian Harmonisation Working Party
AI	Artificial intelligence
AIMDD	Active Implantable Medical Device Directive
AMDE	Adverse medical device event
CA	Competent authority
CAB	Conformity assessment body
CAMD	Competent Authorities for Medical Devices
CAP	Conformity assessment procedure
CAPA	Corrective actions and preventive actions
CEAR	Clinical Evaluation Assessment Report
CECP	Clinical Evaluation Consultation Procedure
CEN	European Committee for Standardization
CENELEC	European Electrotechnical Committee for Standardization
CER	Clinical evaluation report
CIP	Clinical investigation plan
CMR	Carcinogenic, mutagenic or toxic to reproduction
DA	Designating Authority (Notifying Authority)
DoC	Declaration of conformity
EA	European Co-Operation for Accreditation
EC	European Community
ECJ or CJEU	European Court of Justice
ED	Early dialogue
EEC	European Economic Community
EESC	European Economic and Social Committee
EN	European Norm
EP	European Parliament
ER	Essential requirements
ESC	Economic and Social Committee
ESO	European Standardization Organization
ETSI	European Telecommunications Standards Institute
EU	European Union
EUDAMED	EUropean DAtabank on MEdical Devices
EUnetHTA	European Union Network of Health Technology Assessment
FDA	Food and Drug Administration (US)
FMEA	Failure mode and effects analysis

FSCA	Field safety corrective action
FSN	Field safety notice
GATT	General Agreement on Tariffs and Trade
GHTF	Global Harmonisation Task Force
GMDN	Global Medical Device Nomenclature
GSPR	General safety and performance requirements
HIQA	Health Information and Quality Authority
HPRA	Health Products Regulatory Authority
HS	Harmonised standard(s)
HSE	Health Service Executive
HSE HBS	Health Service Executive Health Business Services
HTA	Health Technology Assessment
HTAB	Health Technology Assessment Body
ICIJ	International Consortium of Investigative Journalists
IFU	Instructions for use
IMDRF	International Medical Devices Regulators Forum
ISO	International Organization for Standardization
IVDMDD	*In-vitro* Diagnostic Medical Device Directive
IVDs	*In-vitro* diagnostic medical devices
KCE	Belgian Healthcare Knowledge Centre
LMIC	Low-to-middle income country
MAUDE	Manufacturer and User Facility Device Experience (FDA)
MD-PS	medical device-related patient safety
MDD	Medical Device Directive (Council Directive 93/42/EEC)
MDR	Medical Device Regulation (Regulation (EU) 2017/745)
MHPRA	Medicines and Healthcare Products Regulatory Agency (UK)
MOM	metal-on-metal (usually referring to a hip implant)
MRA	Mutual Recognition Agreement
MS	Member state/s
NAB	National accreditation body
NB	Notified body
NBOG	Notified Bodies Operations Group
NCA	National competent authority
NCAR	National Competent Authority Report
NLF	New Legislative Framework
OECD	Organisation for Economic Co-operation and Development
OJ	Official Journal
OJEU	Official Journal of the European Union

OLP	Ordinary legislative procedure
PAHO	Pan American Health Organization
PIP	Poly Implant Prothèse (breast implant)
PLEG	Post-launch evidence generation
PMA	Pre-market approval
PMCF	Post-market clinical follow-up
PMS	Post-market surveillance
PSUR	Periodic safety update report
QDA	Qualitative document analysis
QES	Qualitative evidence synthesis
QMS	Quality management system
RCT	Randomised controlled trial
REC	Research Ethics Committee
RMS	Risk management system
RWD	‘real world data’
RWE	‘real world evidence’
SaMD	Software as a medical device
SME	Small to medium enterprise
SRN	Single registration number for an economic operator
SSCP	Summary of Safety and Clinical Performance
TC	Technical Committee
TD	Technical documentation
TDAR	Technical Documentation Assessment Report
TED	Tenders Electronic Daily
TEU	Treaty on European Union
TFEU	Treaty on the Functioning of the European Union
TGA	Therapeutic Goods Administration
UDI	Unique device identification
UDI-DI	Unique device identification - device identifier
UDI-PI	Unique device identification - production identifier
UN	United Nations
US	United States of America
WHO	World Health Organization
WTO	World Trade Organization

Glossary of Terms

Term	Definition
Accessory for a medical device	means an article which, whilst not being itself a medical device, is intended by its manufacturer to be used together with one or several particular medical device(s) to specifically enable the medical device(s) to be used in accordance with its/their intended purpose(s) or to specifically and directly assist the medical functionality of the medical device(s) in terms of its/their intended purpose(s);*
Accreditation	an attestation by a national accreditation body that a conformity assessment body meets the requirements set by harmonised standards and, where applicable, any additional requirements including those set out in relevant sectoral schemes, to carry out a specific conformity assessment activity;**
Accreditation body	means the sole body in a Member State that performs accreditation with authority derived from the State as laid down by Article 2(10) of Regulation (EC) No 765/2008.**
Active device	means any device, the operation of which depends on a source of energy other than that generated by the human body for that purpose, or by gravity, and which acts by changing the density of or converting that energy. Devices intended to transmit energy, substances or other elements between an active device and the patient, without any significant change, shall not be deemed to be active devices. Software shall also be deemed to be an active device;*
Adverse event	means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device;*
Adverse medical device events (AMDEs)	Any patient harm caused by device-related medical or surgical management rather than the patient's illness'.«
Authorised representative	means any natural or legal person established within the Union who has received and accepted a written mandate from a manufacturer, located outside the Union, to act on the manufacturer's behalf in relation to specified tasks with regard to the latter's obligations under this Regulation;*
Benefit-risk determination	means the analysis of all assessments of benefit and risk of possible relevance for the use of the device for the intended purpose, when used in accordance with the intended purpose given by the manufacturer;*
CE marking	a marking by which the manufacturer indicates that the product is in conformity with the applicable requirements set out in Community harmonisation legislation providing for its affixing;**

Clinical benefit	means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health;*
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;*
Clinical evaluation	means a systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer;*
Clinical evidence	means clinical data and clinical evaluation results pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer;*
Clinical investigation	means any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device;*
Clinical investigation plan	means a document that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of a clinical investigation;*
Clinical performance	means the ability of a device, resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its intended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for patients, when used as intended by the manufacturer;*
Common specifications (CS)	means a set of technical and/or clinical requirements, other than a standard, that provides a means of complying with the legal obligations applicable to a device, process or system.*
Community harmonisation legislation	any Community legislation harmonising the conditions for the marketing of products.**

Compatibility	is the ability of a device, including software, when used together with one or more other devices in accordance with its intended purpose, to: (a) perform without losing or compromising the ability to perform as intended, and/or (b) integrate and/or operate without the need for modification or adaption of any part of the combined devices, and/or (c) be used together without conflict/interference or adverse reaction.*
Competent authority	means the authority(ies) in charge of market surveillance and/or of vigilance for devices;***
Conformity assessment	is the process demonstrating whether specified requirements relating to a product, process, service, system, person or body have been fulfilled;**
Conformity assessment body	means a body that performs third-party conformity assessment activities including calibration, testing, certification and inspection; (when notified to the Commission they are referred to as notified bodies, NBs)*
Corrective action	means action taken to eliminate the cause of a potential or actual non-conformity or other undesirable situation;*
Custom-made device	means any device specifically made in accordance with a written prescription of any person authorised by national law by virtue of that person's professional qualifications which gives, under that person's responsibility, specific design characteristics, and is intended for the sole use of a particular patient exclusively to meet their individual conditions and needs. However, mass-produced devices which need to be adapted to meet the specific requirements of any professional user and devices which are mass-produced by means of industrial manufacturing processes in accordance with the written prescriptions of any authorised person shall not be considered to be custom-made devices;*
Designating authority	means the authority(ies) entrusted by a Member State to assess, designate, notify and monitor notified bodies under Directive 90/385/EEC or Directive 93/42/EEC;***
Device deficiency	means any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer;*
Distributor	means any natural or legal person in the supply chain, other than the manufacturer or the importer, that makes a device available on the market, up until the point of putting into service;*
Draft standard	document containing the text of the technical specifications concerning a given subject, which is being considered for adoption in accordance with the national standards procedure, as that document stands after the preparatory work and as circulated for public comment or scrutiny;^

Draft technical regulation	the text of a technical specification including administrative provisions, formulated with the aim of enacting it or of ultimately having it enacted as ' a technical regulation, the text being at a stage or preparation at which substantial amendments can still be made;^
Economic operator	means a manufacturer, an authorised representative, an importer, a distributor or the person referred to in Article 22(1) and 22(3) [of the MDR];*
Effectiveness	'The benefit of using a technology, programme or intervention to address a specific problem under general or routine conditions, rather than under controlled conditions, for example, by a physician in a hospital or by a patient at home.'°
Efficacy	'The benefit of using a technology, programme or intervention to treat a particular problem under ideal conditions—for example, in the context of research in a laboratory or a rigourous protocol for a randomized clinical trial.'°
Ethics committee	means an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of this Regulation, taking into account the views of laypersons, in particular patients or patients' organisations;*
Field safety corrective action (FSCA)	means corrective action taken by a manufacturer for technical or medical reasons to prevent or reduce the risk of a serious incident in relation to a device made available on the market;*
Field safety notice	means a communication sent by a manufacturer to users or customers in relation to a field safety corrective action;*
Harmonised standard	means a European standard as defined in point (1)(c) of Article 2 of Regulation (EU) No 1025/2012; [i.e. a European standard adopted on the basis of a request made by the Commission for the application of Union harmonisation legislation]*
Implantable device	means any device, including those that are partially or wholly absorbed, which is intended: — to be totally introduced into the human body, or — to replace an epithelial surface or the surface of the eye, by clinical intervention and which is intended to remain in place after the procedure. Any device intended to be partially introduced into the human body by clinical intervention and intended to remain in place after the procedure for at least 30 days shall also be deemed to be an implantable device;*
Importer	means any natural or legal person established within the Union that places a device from a third country on the Union market;*
Incident	means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error

	due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect;*
Informed consent	means a subject's free and voluntary expression of his or her willingness to participate in a particular clinical investigation, after having been informed of all aspects of the clinical investigation that are relevant to the subject's decision to participate or, in the case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical investigation;*
Instructions for use	means the information provided by the manufacturer to inform the user of a device's intended purpose and proper use and of any precautions to be taken;*
Intended purpose	means the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the manufacturer in the clinical evaluation;*
Interoperability	is the ability of two or more devices, including software, from the same manufacturer or from different manufacturers, to: (a) exchange information and use the information that has been exchanged for the correct execution of a specified function without changing the content of the data, and/or (b) communicate with each other, and/or (c) work together as intended.*
Invasive device	means any device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body;*
Investigational device	means a device that is assessed in a clinical investigation;*
Investigator	means an individual responsible for the conduct of a clinical investigation at a clinical investigation site;*
Making available on the market	means any supply of a device, other than an investigational device, for distribution, consumption or use on the Union market in the course of a commercial activity, whether in return for payment or free of charge;*
Manufacturer	means a natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark;*
Market surveillance	means the activities carried out and measures taken by competent authorities to check and ensure that devices comply with the requirements set out in the relevant Union harmonisation legislation and do not endanger health, safety or any other aspect of public interest protection;*
Market surveillance	an authority of a Member State responsible for carrying out market surveillance on its territory;**

authority (Competent Authorities)	
Medical Device – definition according to the MDD	‘A medical device is any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of: – diagnosis, prevention, monitoring, treatment or alleviation of disease, – diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap, – investigation, replacement or modification of the anatomy or of a physiological process, – control of conception and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.’^^
Medical device – definition according to the MDR	means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes: — diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, — diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability, — investigation, replacement or modification of the anatomy or of a physiological or pathological process or state, — providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, 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. The following products shall also be deemed to be medical devices: — devices for the control or support of conception; — products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.*
Nanomaterial	means a natural, incidental or manufactured material containing particles in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or

	more external dimensions is in the size range 1-100 nm; Fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below 1 nm shall also be deemed to be nanomaterials;*
National Accreditation Body	the sole body in a Member State that performs accreditation with authority derived from the State;**
Non-viable	means having no potential for metabolism or multiplication;*
Notified body	means a conformity assessment body which has been notified by a Member State in accordance with Article 11 of Directive 90/385/EEC or Article 16 of Directive 93/42/EEC; [or in accordance with Regulation (EU) 2017/745]*
Notifying Authority (Designating Authority)	An authority designated by a member state to 'be responsible for setting up and carrying out the necessary procedures for the assessment and notification of conformity assessment bodies and the monitoring of notified bodies, including compliance with the provisions of Article [R20].****
Observed audit	means a designating authority's assessment of the performance of a notified body's audit team in the premises of the body's client;***
On-site assessment	means a verification in the premises of the body or of one of its subcontractors or subsidiaries by the designating authority;***
Patient safety	The prevention of errors and adverse effects to patients associated with health care.°°
Peer evaluation	a process for the assessment of a national accreditation body by other national accreditation bodies, carried out in accordance with the requirements of this Regulation, and, where applicable, additional sectoral technical specifications;**
Performance	means the ability of a device to achieve its intended purpose as stated by the manufacturer;*
Placing on the market	means the first making available of a device, other than an investigational device, on the Union market;*
Post-market surveillance	means all activities carried out by manufacturers in cooperation with other economic operators to institute and keep up to date a systematic procedure to proactively collect and review experience gained from devices they place on the market, make available on the market or put into service for the purpose of identifying any need to immediately apply any necessary corrective or preventive actions;*
Procedure pack	means a combination of products packaged together and placed on the market with the purpose of being used for a specific medical purpose;*
Product	industrially manufactured products other than agricultural products within the meaning of Article 38 (1) of the Treaty, products for human or animal consumption, medicinal products within the meaning of Directive

	65/65/EEC (2) and cosmetic products within the meaning of Directive 76/768/EEC (2).^
Putting into service	means the stage at which a device, other than an investigational device, has been made available to the final user as being ready for use on the Union market for the first time for its intended purpose;*
Recall	means any measure aimed at achieving the return of a device that has already been made available to the end user;*
Reprocessing	means a process carried out on a used device in order to allow its safe reuse including cleaning, disinfection, sterilisation and related procedures, as well as testing and restoring the technical and functional safety of the used device;*
Risk	means the combination of the probability of occurrence of harm and the severity of that harm;*
Safety	The reduction of risk of unnecessary harm to an acceptable minimum.««
Serious adverse event	means any adverse event that led to any of the following: (a) death, (b) serious deterioration in the health of the subject, that resulted in any of the following: (i) life-threatening illness or injury, (ii) permanent impairment of a body structure or a body function, (iii) hospitalisation or prolongation of patient hospitalisation, (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, (v) chronic disease, (c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect;*
Serious incident	means any incident that directly or indirectly led, might have led or might lead to any of the following: (a) the death of a patient, user or other person, (b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health, (c) a serious public health threat;*
Serious public health threat	means an event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time;*
Single-use device	means a device that is intended to be used on one individual during a single procedure;*

Sponsor	means any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation;*
Standard	a technical specification approved by a recognized standardizing body for repeated or continuous application, with which compliance is not compulsory.^
Standards programme	document listing the subjects for which it is intended to draw up or alter a standard.^
Subcontracting	means the transfer of tasks to one of the following: (i) a legal person; (ii) a natural person who further delegates these tasks or parts thereof; (iii) several natural or legal persons who jointly perform these tasks.***
Subject	means an individual who participates in a clinical investigation;*
Surveillance on-site assessment	means a periodic routine on-site assessment which is neither the on-site assessment undertaken for the initial designation, nor the on-site assessment undertaken for the renewal of the designation.***
System	means a combination of products, either packaged together or not, which are intended to be inter-connected or combined to achieve a specific medical purpose;*
Technical regulation	technical specifications, including the relevant administrative provisions, the observance of which is compulsory, de jure or defacto, in the case of marketing or use in a Member State or a major part thereof, except those laid down by local authorities.^
Technical specification	a specification contained in a document which lays down the characteristics required of a product such as levels of quality, performance, safety or dimensions, including the requirements applicable to the product as regards terminology, symbols, testing and test methods, packaging, marking or labelling.^
Unique Device Identifier (UDI)	means a series of numeric or alphanumeric characters that is created through internationally accepted device identification and coding standards and that allows unambiguous identification of specific devices on the market;*
User	means any healthcare professional or lay person who uses a device;
Vigilance	Reporting of serious incidents and FSCAs by manufacturers to the relevant competent authorities. It is a reactive process.˚˚˚
Withdrawal	means any measure aimed at preventing a device in the supply chain from being further made available on the market;*

Sources: *Regulation (EU) 2017/745 (MDR); **Regulation (EC) No 765/2008; ***Commission Implementing Regulation(EU) No 920/2013 of 24 September 2013; ****Decision 768/2008/EC; ^Council Directive 83/189/EEC; ^^Council Directive 93/42/EEC (MDD); ˚https://htaglossary.net/HomePage; ˚˚https://www.who.int/news-room/fact-sheets/detail/patient-safety; ‟Samore et al, 2004, p.326; ‟‟Runciman et al, 2009, p.21.

1. Introduction

This thesis is concerned with exploring the safety of medical devices and the causes or contributory factors leading to patient harm. These causes and contributory factors may arise at any stage in the life of a medical device, so this research is necessarily broad in its scope, but focusses on those aspects that have the potential to be improved through policy intervention. To narrow its scope, yet still concentrate on high-risk devices, it focusses primarily on non-active implantable medical devices used in Europe[i]. However, many of the findings from this research are also applicable to other types of medical device, therefore, the term 'medical device' or 'device' will be used throughout the thesis and only where it refers more specifically to implantable devices will this be stated.

The research was conducted in the context of a changing regulatory framework for medical devices in Europe, with the enactment of the two Medical Device Regulations (MDRs, which consist of the *In-vitro* Diagnostic Device Regulation,[2] the IVDR, and the Medical Device Regulation,[3] the MDR) in 2017 by the European Union (EU), and the entry into force of the first of these in 2021. At the time of writing, the previous Medical Device Directives (MDDs) are still in force,[1,4,5] being phased out gradually as the MDRs come into full force. It was also conducted within the context of a global pandemic (Covid-19), which brought many changes across the globe. Amongst these, it affected the implementation of the new regulatory framework, and it also altered the way this research was conducted.

The motivation behind this research project arose from a dawning recognition that the safety of medical devices is largely unknown, with many people assuming that only devices that are safe and effective are allowed to enter the healthcare system. This, together with the realisation that there is no comprehensive, systematic collection of data on implanted devices for analysis or evidence synthesis to enable people to make informed choices, not even the surgeons implanting them, motivated me to try to find ways of improving medical device safety through policy-focussed research with a transformative agenda. It was fuelled by the high-profile device 'failures' in the last couple of decades that came to international attention because of the severe effects they had on patients' health.[6] Clearly, the regulation of medical devices in the EU, and indeed globally, does not ensure that devices on the market are safe and effective. The vision for the research was to find ways in which medical device safety could be improved. It

[i] Medical devices are products used in healthcare that work primarily through physical means, whilst non-active devices are those that do not rely on any external energy source, such as electricity or batteries, to function. Medical devices that are introduced into the body and remain there for thirty days or more are classed as implantable devices.[1, Article 1.2(a) and Annex IX 1.1-1.6]

focusses largely on the stages and processes that occur before a device enters clinical practice, because prevention is better than cure.

Apart from academia, the intended audiences for this research are policymakers, Health Technology Assessment (HTA) bodies (HTABs), medical device regulators, and clinicians interested in improving medical device safety for their patients.

1.1. Background to the research

Modern healthcare relies heavily on advances in technology to improve health and to alleviate suffering in ways that were not available in the past.[7–10] However, despite major advances in healthcare, safety remains an issue.[11,12] Indeed, some medical devices that were assumed to be safe have resulted in catastrophic failures.[13–15] These failures have brought medical device safety into the spotlight, highlighting issues in the regulatory processes controlling the marketing of medical devices and demonstrating the system's weaknesses in preventing or detecting adverse medical device events (AMDEs).[16–19]

1.1.1. Underreporting of AMDEs is a global phenomenon.

The Research Priority Setting Working Group of the World Alliance for Patient Safety highlighted the lack of information available on AMDEs globally, including information on the epidemiology of such events, recognition and reporting, and the structures and processes around AMDEs.[20] This means that both the pre-market and the post-market evidence generation mechanisms are inadequate. Consequently, they argue that better data is needed on the structures, processes and patient outcomes from countries at all stages of development, to reduce the rate and extent of harm.[20] That was in 2008. Yet the gaps remain. Therefore, a review of the processes involved was considered necessary to understand why better evidence is not available for clinical decision-making, with a particular focus on the regulatory process, since it clearly fails to ensure the safety of medical devices on the market.

1.2. Aims of the Project

The overarching aim of this research was to identify key risk factors to medical device safety within a European context by examining the medical device lifecycle, particularly its regulation, and potential policy solutions for improving device safety.

To do this it was necessary to understand the various lifecycle processes[i]. However, there are a multiplicity of ways in which the medical device lifecycle is characterised and

[i] I assumed[i] that if the different processes could be understood (including their potential risks and safeguards against error) and explained in lay language, then all stakeholders could understand these processes, and that should reduce the risk of harms that might occur because of wrong assumptions being made leading to misinformed decision-making. However, later in the research it became clear that not all decisions are evidence-informed, and that in fact, evidence might not change decision-making at all.

many different processes and subprocesses involved. Therefore, as a first step, to clarify which processes were most important to examine, a review of lifecycle models was needed. As the research progressed it became clear that the most important process for ensuring device safety is the regulatory process. Consequently, this became the primary focus of the research.

Therefore, the research questions that this thesis addresses are:

1. What lifecycle approaches, models or frameworks have been used to evaluate medical devices? What is meant by the 'medical device lifecycle' and 'lifecycle evaluation'? How do these differences in meanings affect patient safety?
2. How are medical devices regulated? And how does this affect patient safety?

To answer these questions two main studies were conducted. The first, a literature review, is a qualitative synthesis of lifecycle evaluation models used by various actors across the medical device lifecycle. The second, a documentary analysis, is a qualitative analysis of the regulatory process for medical devices, particularly in the European Union (EU).

In addition, an overview of some of the other key lifecycle processes is provided in Chapter 6 to situate the importance of medical device regulation, and a review of regulatory theory, which was used to focus the documentary analysis and to guide interpretation of the regulatory process for medical devices, is provided in Chapter 4,.

For simplicity, these are referred to throughout the thesis as the lifecycle review, the process review, regulatory theory, and the regulation review chapters.

1.3. Key definitions

Key concepts and other important terms are defined in the Glossary of Terms to clarify the meanings attributed to them for the purposes of this research and referred to throughout the thesis with footnotes or an asterisk, indicating that it is defined in the glossary. However, this section defines two key concepts for the thesis overall, the medical device and patient safety.

1.3.1. What is a medical device?

The legal definition of a medical device varies according to the different jurisdictions, nevertheless, most jurisdictions would consider a medical device to be any entity with a physical mode of action that is used to diagnose, prevent, monitor, treat, alleviate, or rehabilitate disease or disability, or control conception. This research has used the EU

definition as stated in Council Directive 93/42/EEC on medical devices[i] (Box 1.1), also known as Directive 93/42/EEC or the MDD.[1]

> *'A medical device is any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:*
>
> – *diagnosis, prevention, monitoring, treatment or alleviation of disease,*
> – *diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,*
> – *investigation, replacement or modification of the anatomy or of a physiological process,*
> – *control of conception*
>
> *and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.'*[1]

Box 1.1: Definition of a medical device according to Directive 93/42/EEC

The Medical Device Directive (MDD) uses a risk-based classification for medical devices which primarily depends on the device's intended use, degree of invasiveness, and duration of patient contact.[1] Devices are assigned to one of four risk categories, which, from lowest to highest risk, are: Class I, Class IIa, Class IIb, and Class III (Table 1.1).[1] The degree of regulatory 'scrutiny' applied to a medical device is dependent on its classification, with greater scrutiny applied to the higher risk devices. Class I devices are further classified according to whether they require sterilisation before use (Class I_s) or if they have a measuring function (Class I_m) and so require calibration, both of which require greater scrutiny and must comply with additional requirements over those normally expected of Class I devices, but only for those aspects related to the sterilisation or measurement function, whichever applies. Most implantable devices fall into Class IIb or III.

Table 1.1: EU Classification of Medical Device

Risk	Low	Medium	High	Highest
Class	I	IIa	IIb	III

[i] The reason for choosing the definition in the MDD rather than the MDR is that the original intention was to have completed this thesis by the time the MDR came into force, and, consequently, the focus of the analysis was largely on the MDD.

1.3.2. What is patient safety?

Patient safety is explored in greater detail later in the thesis, but for now the working definitions are presented in Box 1.2. It is worth noting that the concept of patient safety is often used to mean its opposite (i.e. patient harm). For example, when people attempt to measure patient safety often what is measured is the absence, or the level, of patient harm.

The World Health Organization (WHO) defines safety as *'the reduction of risk of unnecessary harm to an acceptable minimum'*.[21,22 p.21] Patient safety is defined as *'the prevention of errors and adverse effects to patients associated with health care'*.[23,24] Adverse medical device events (AMDEs) may be considered to be *'any patient harm caused by device-related medical or surgical management rather than the patient's illness'*.[25 p.326]

Box 1.2: Defining safety and harm

Furthermore, since the purpose of healthcare is to provide effective treatments, the provision of ineffective treatment is itself a healthcare-related error, consequently, for the purpose of this research a lack of efficacy or effectiveness is also considered to be a patient safety issue and is included within the concept of patient safety. Thus, for a device to be considered safe it must also be efficacious and effective (as defined in Box 1.3). Therefore, I conceptualise medical device safety as encompassing efficacy and effectiveness throughout this thesis.

Efficacy is defined as *'The benefit of using a technology, programme or intervention to treat a particular problem under ideal conditions—for example, in the context of research in a laboratory or a rigourous protocol for a randomized clinical trial.'* [26] Effectiveness is defined as *'The benefit of using a technology, programme or intervention to address a specific problem under general or routine conditions, rather than under controlled conditions, for example, by a physician in a hospital or by a patient at home.'* [27]

Box 1.3: Defining efficacy and effectiveness

1.4. Overall research approach

The research proceeded in phases, iteratively focussing on the processes most likely to introduce risks to medical device-related patient safety (MD-PS) or with the greatest possibility of being amenable to reducing risks through policy intervention. Together with developing the necessary methods, three main studies were conducted concurrently. The research phases did not coincide with individual studies, rather the three studies

were expanded or reduced as it became clearer where the problems lay that most needed addressing and were policy-amenable. The first was a review of conceptual or theoretical models of the medical device lifecycle, initially conducted to identify a framework for exploring the medical device lifecycle processes. This study expanded when it became clear that differences in meaning between actors involved in the medical device lifecycle regarding what a medical device lifecycle encompasses and differing motivations for conducting a lifecycle evaluation were themselves MD-PS factors. The second study is a qualitative descriptive study that included a grey literature review of guidelines, textbooks, standards, and other documents to identify how key processes should be performed and interviews with key informants to understand how these processes were conducted in practice. This study's scope was reduced as it became clear that the key processes impacting patient safety are those related to the design, manufacture, and sale of medical devices, but more particularly, how medical devices are regulated. The third study is a documentary analysis of legislation and other relevant regulatory or policy documents exploring how the regulation of medical devices is conducted. This study expanded as it became clear that how medical devices are regulated now has followed a certain (almost unescapable) historical trajectory, understanding which highlights the root causes of a complicated, fragmented, and confidential system that prevents the necessary evidence to assess the safety and effectiveness of devices being available to base evidence-based clinical (and reimbursement) decisions on, which is a significant cause of MD-PS problems. This study, therefore, refocussed to examine not just how the EU medical device regulatory process functions, but also why it is the way it is. The research phases are illustrated in Figure 1.1.

1.1. What the research shows

The lifecycle review revealed that different people understand different things when using the same words for concepts such as the 'medical device lifecycle' and 'lifecycle evaluation'. This meant that the goals for utilising and promoting a lifecycle approach to evaluating medical devices remain hidden, as do the consequences of adopting such an approach. The adoption of a lifecycle approach by the regulators has meant that they are willing to accept limited evidence of safety and device performance or efficacy in the pre-market phase for most devices, relying on post-market activity to reveal which devices are not so effective or as safe as others, even though most post-market data collection concentrates on harms rather than efficacy/effectiveness. It also meant the adoption of a risk-based approach to regulation, which classifies devices according to their perceived level of risk, with the consequent application of specified regulatory

requirements considered to be proportionate to that risk. However, risk is not the same as actual harm, nor is 'benefit' the same as effectiveness, both of which can only be assessed by evaluating patients' outcomes. Furthermore, post-market surveillance (PMS) generally relies on incident reporting, which is notoriously poor, and no nation appears to have adopted a pro-active, comprehensive, and systematic approach to collecting data on patient outcomes related to medical devices through which it might be possible to estimate and compare their efficacy and safety, not even for all implantable devices[i]. Having successfully pressured the regulators into accepting this limited evidence, pressure is now being applied to policymakers, HTABs, and clinicians to adopt a lifecycle approach accepting limited evidence for the procurement and use of devices, arguing that this evidence is better gathered in the post-market phase as demands for rigorous evidence in the pre-market phase or pre-purchase impose too heavy a burden on small-to-medium enterprises (SMEs), thereby limiting patient access to beneficial innovations.

The regulation review revealed that the EU regulatory framework for medical devices was never intended for patient protection, but rather for removing barriers to trade caused by differing safety regulations amongst the member states (MS). Specific risks are attended to through a risk management process that is intended to minimise the risk to an acceptable level when compared with the anticipated benefits of the device, as determined by the manufacturer. Medical devices in the EU are not authorised for sale, instead, their compliance with the regulatory requirements is assessed, in a conformity assessment procedure, by independent, frequently for-profit organisations who are designated as competent to perform these procedures. These notified bodies are contracted by manufacturers to perform the conformity assessment procedure, following which they approve the affixing of the CE marking (necessary for the legal placement of a device on the EU market) on the device and/or its packaging and issue a certificate of compliance. The regulatory system is fragmented, lacks transparency, and the evidence upon which a device is allowed onto the EU market is mostly confidential. This makes it difficult to uncover the truth and conceals how poorly regulated medical devices are, whilst at the same time falsely reassuring the public that medical device regulation is rigorous. It also conceals how much influence industry has on medical device regulation, which it has effectively captured for its own interests. Furthermore, this is not simply an EU problem, it is a global phenomenon.

[i] Although some nations or specialities have set up registries for specific types of implantable device, such as large joints (hip, knee, shoulder), breast implants, and cardiac implantable devices, but these have largely been established in response to serious device failures or the recognition of the need for more data on them by the clinical specialists involved.

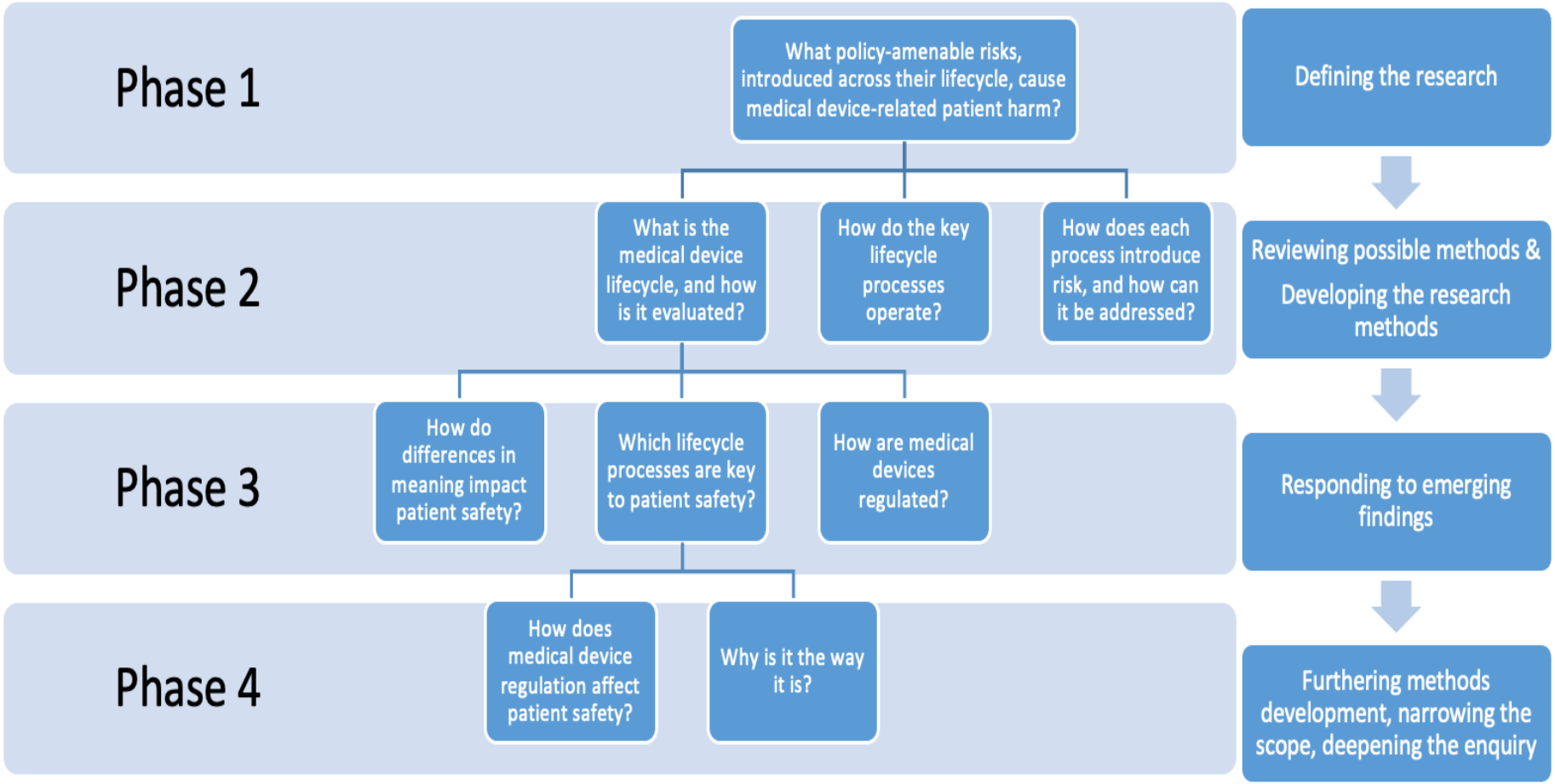


Figure 1.1. Phases of research

1.2. Contribution to knowledge

The World Health Alliance for Patient Safety identified a need for better data on patient safety, which this research has sought to address by exploring the underlying reasons for the lack of available data.[20] This research contributes to original knowledge by adopting the systems approach proposed by Balka et al to expose lifecycle-based systemic risks to patient safety that are introduced beyond the healthcare system, and that are, therefore, beyond its capacity to address.[28] Similar to Horvath's analysis of the FDA's approach to regulating medical devices, where he concludes that they are *'[t]rading safety for innovation and* access',[29, p.991] it finds that the EU has adopted a similar regulatory trade-off. It reveals assumptions and underlying forces that continue to conceal these risks, demonstrating a need for policymakers to reconsider how they balance competing policy objectives. Specifically, it shows that current approaches to maintaining and promoting trade have untoward effects on healthcare, impacting patient and healthcare system outcomes.

Specifically, it uncovers key risks that require policy intervention across the medical device lifecycle by illuminating dangerous assumptions, potential modes of system failure, and how these may remain undetected yet cause untoward and undocumented harm to patients. Further, it exposes the inadequacies of the regulatory process at safeguarding patients and the reasons why this is so, exposing industry's capture of the regulatory process and highlighting the need to demand better regulation and better evidence in the pre-market and post-market stages.

From a methodological perspective, it contributes a novel method for reviewing conceptual models and frameworks and a novel approach to analysing legislation and legal documents for the purpose of exploring the dynamics at play and who wields the power.[i]

In addition, during the course of the PhD I have conducted a rapid mixed-methods study on collaboration between independent HTA and public procurement bodies to support the HTA function in Ireland (2017-2018), and I have collaborated on a project with the Belgian Healthcare Knowledge Centre (KCE) examining the level of evidence available on medical devices (and medicines) at market entry or at the point of initial request for reimbursement in the EU (2019-2023).[30,31][ii]

[i] These draw on Coglianese's four core components of regulation (section 4.6)

[ii] The PhD process also contributed to me as a researcher by enabling me to become proficient in qualitative research methods and statistical analytic packages. Other contributions include projects I've participated in, for which some details and their outputs are provided in Appendix 14.1.

1.3. Outline of the thesis

The remainder of this thesis is set out in ten chapters. Chapter 2 is a literature review, providing background information, describing the importance of patient safety, and explaining why this research was needed, including the rationale for the research approach taken. Chapter 3 describes the methodology and the underlying conceptual framework guiding the overall research project. Chapter 4 explores regulatory theory, setting out the theories and conceptual framework underpinning the regulation review. Chapter 5 describes the research methods and their development. Chapter 6 provides the findings from the Lifecycle Review. Chapter 7 provides an overview of some key lifecycle processes. The findings from the Regulation Review are divided amongst Chapters 8-10. Chapter 8 provides a narrative overview of medical device regulation in a global context describing the key institutional actors involved globally and at the EU level, detailing the evolving history of the European institutions. Chapter 9 explains the legal procedures involved in enacting the original and the revised medical device legal frameworks and describes the legislative history that led up to the enactment of the MDD and subsequent developments prior to its revision, ending with a brief overview of the structure and contents of the MDD. Chapter 10 focusses on the implementation of the MDD and the MDR and the outcomes of these. It describes the actors involved and the implementation process. The research findings and its limitations are discussed in Chapter 11, including implications for research, policy, and practice. Chapter 12 concludes the thesis, with a brief summary of key findings and a series of recommendations. The subsequent chapters, 13 and 14, contain the references and appendices, respectively.

In view of the complexity and diversity of subjects within this research project, figures, tables and boxes have been used to signpost and summarise preceding and proceeding sections in the hope of making navigation clearer.

2. Literature Review

The following literature review examines some of the difficulties and challenges with evaluating medical device safety and the approaches taken by various researchers to overcoming these, demonstrating the gaps that this research sought to address and explaining the approach taken.

2.1. Medical device safety is a significant issue

Patient safety is a serious issue for implantable medical devices.[14,15,32–35] Furthermore, a medical device may be ineffective or less effective than an alternative treatment, thereby causing harm by displacing an effective therapy and, in the case of implantable devices, unnecessarily exposing patients to the risks of surgery, whilst also causing unwarranted costs to the healthcare service.[36,37]

How much of a problem it poses is largely unknown. [25,38–40] Efforts to estimate the size of the problem have been stymied by lack of data, both in terms of denominators and numerators. We don't know how many devices there are on the market, how many people are implanted with them, or what patients' outcomes are, nor what they would have been without the implant. Furthermore, there is no standardised approach to reporting adverse medical device events (AMDEs), which makes it difficult to aggregate the data.[28] Nevertheless, Table 2.1 illustrates some attempts to estimate the rate of AMDEs associated with medical devices in different contexts using different ascertainment methods. It demonstrates that, whilst we do not know the full extent of this problem, it is, nevertheless, sizeable, potentially enormous, and remains largely hidden.

Furthermore, it is a rapidly growing problem, as demonstrated by Table 2.2, which summarises data gathered by Bowers and Cohen from nineteen EU MS national competent authorities on incidents reported to them over the last few years.[41] They report a doubling to fourfold increase in medical device incident reporting to individual countries, with Germany experiencing a threefold increase over nine years and Italy experiencing a fourfold increase in just four years.

Table 2.1: Summary overview: Estimates of Adverse Medical Device Events

Author, Year[citation]: Study period	Setting: Population; Device types	Data Source/Methods	Estimated AMDE rate
Samore et al, 2004[25]: Jan-Sep 2003	US, 520-bed hospital: Hospital in-patients and Day patients; All	A combination of passive and active surveillance methods including: Online Incident Event Reporting; Computer-Flag–Based Surveillance; Telemetry Checklist; ICD-9-Code–Based Surveillance; Post-discharge Patient Survey; Clinical Engineering Database.	83.7 AMDEs/1000 admissions.
Hefflin et al, 2004[42]: Jul 1999 – Jun 2000	US, Emergency Departments (EDs): A nationally representative, stratified sample of hospital emergency departments; All	Random sample of NEISS† case reports that involved medical device products (10,395 medical device–associated adverse events).	454,383 AMDE-related visits/12 months.
Wang et al, 2010[43]: 01 Jan 2004 – 31 Dec 2005	US, Nationally representative sample ~ 67 hospital EDs: All paediatric patients who visited a NEISS All Injury Program (AIP) ED because of AMDEs; All	AMDE-related NEISS case reports.	Estimated 144,799 paediatric AMDE-related ED visits/24-months (95% CI: 113,051–183,903): ~72,400 annually.
Myers, Jones, & Sittig, 2011[44]: 1984 – 31 Mar 2010	US, Setting not specified: No specific population; Clinical Information Systems (CIS)	Medical Device Reporting, MAUDE†, and Medical Product Safety Network (MedSun) databases	210 reports over 18 years, plus 200 other reports and 164 Blood Bank Reports not included in the study.
Brady et, 2013[45]: 2004-2011	US, 44 paediatric hospitals: Paediatric in-patients; Device type not specified	Pediatric Health Information System (PHIS).	3.3% of hospitalised children.
Cooper et al, 2015[39]: 01 Jan 2000-01 Aug 2012	US, Setting not specified: Patients receiving robotic surgery; Robotic surgery devices	FDA MAUDE† database, LexisNexis, and PACER (Public Access to Court Electronic Records).	245 events were reported to the FDA (71 deaths and 174 nonfatal injuries) plus 5 additional events were not reported (including one device-associated patient death).

Hwang et al, 2016[46]: CE marking: 2005-2010; Recall notices up to Jan 2016	US, Setting not specified: Patients with cardiological, neurological and orthopaedic conditions; High-risk cardiological, neurological and orthopaedic devices newly receiving CE marking	Food and Drug Administration (FDA), the Medicines and Healthcare Products Regulatory Agency (MHPRA), and the Bundesinstitut für Arzneimittel und Medizinprodukt (BfArM) databases.	309 new CE markings: 76 recalls/PMS safety alert = 24%.
Gagliardi et al, 2017[47]: 2005-2015	Canada, No specific setting: No specific population; Licensed medical devices, Classes II, III and IV	Medical Devices Active Licence Listing (MDALL) for unique device IDs and the Recall and Safety Alerts Database (RSAD) for recalls.	7,382 recalls/FSNs affecting 13,192 unique device IDs: 5% serious; 60% temporary harm; 35% no harm.
Madi et al, 2018[48]: May 2016	South Africa, 1068-bed tertiary-level urban public sector hospital in Johannesburg: No specific population; Manual & Automatic external defibrillators (MEDs & AEDs)	Clinical audit	7 MEDs (4.9%) and 1 AED (0.7%) had critical problems.
Craig, O'Meley, and Carter, 2019[38]: 2014-2017	Australia, ICU: Patients on ventilators; Ventilators	Therapeutic Goods Administration (TGA) AMDE reports, and 'a large public health service' database.	One in 66 patients could potentially be affected by a failed ventilator.
Nackers et al, 2019[49]: 01 Apr 2014 – 30 Apr 2016	US, Single children's hospital in the Midwest: Children with medical complexity (CMC†), referred to a Pediatric Complex Care Program and assisted by at least 1 medical device; Not specified	Hospital's electronic health records (EHRs), and "Care Everywhere" within Epic (Epic System Corp, Verona, WI) to review available EHR data from external health systems.	Among 98 CMC, device-complicated encounters represented 17% of 258 hospitalizations and 31% of 228 ED visits.
Palojoki, Saranto, & Lehtonen, 2019. [50]: 2010-2015	Finland, All specialised and primary healthcare organisations: EHR users; EHR as SaMD	Finnish National Competent Authority	138 EHR-related AMDE reports.

†Automatic external defibrillator; AMDE=Adverse medical device event; CE=Conformité Européenne; CMC=Children with medical complexity; EHR=Electronic Health Record; FDA=Food and Drug Administration; FSN=Field Safety Notice; MAUDE= Manufacturer and User Facility Device Experience; MDALL=Medical Devices Active Licence Listing; MED=Manual external defibrillator; NEISS=National Electronic Injury Surveillance System; SaMD=Software as a medical device.

Table 2.2: Incident trends as reported by Bowers and Cohen 2018[41]

Country	Incidents reported	Increase in rate of reporting from base year	Time period
Germany	14,034	Threefold	9 years
France	18,208	Double	9 years
UK	19,599	Double	9 years
Spain	-	Fourfold	7 years
Italy	-	Fourfold	4 years

The safety of medical devices is also growing in importance due to the rapidly increasing levels of unknown risks as a result of the speed of technological innovation in biomaterials, software, artificial intelligence (AI), and their potential applications in healthcare (e.g. nanotechnology and 3D printing).[51–53] This means that not only do we not know how frequently AMDEs occur, but now there is greater potential for AMDEs that we cannot anticipate. For example, nanotechnology has the potential to interact with the body, not only at the cellular level, but also at the molecular level – a feature that is being used to improve the biocompatibility of medical devices. However, we have no way of knowing what the unanticipated or long-term effects of this will be on patients, which means we don't even know what to look out for.[54–56]

In tandem with this, there is a growing necessity to improve the assessment of the safety of medical devices on the market, because expedited regulatory pathways are allowing novel medical devices to access the healthcare space more quickly with less and less data on their efficacy and safety.[57–59] Devices approved through these expedited pathways have been shown to carry greater risks to patients compared with those that are more rigorously evaluated before market entry.[57–59]

This presents two problems to be addressed – how to improve the evaluation of medical device safety, and how to improve their safety.

2.2. Evaluating medical device safety

The evaluation of medical device safety may be considered to take place over a continuum. Indeed, activities and decisions made during earlier stages in the life of a medical device affect its safety, effectiveness, and costs (also manufacturers' profits), leading many stakeholders to propose that a lifecycle approach be taken to the evaluation of medical devices.[60,61] However, the purpose, means, and data available for evaluation differ according to whether an evaluation is being conducted in the pre-market phase or the post-market phase.

Furthermore, as Ward and Clarkson have shown, AMDEs may be due to error at different stages in the lifecycle, which they categorise into three main types of 'error'

based on the lifecycle stage within which the error arises, namely – design error, manufacture-related error, and user error.[20,62] Healthcare systems around the world are attempting to improve MDPS by focussing on human factors and use error.[63–65] Nevertheless, it is design and/or manufacturing error that most frequently leads to serious harm resulting in market withdrawal.[66–72] Therefore, efforts to reduce harm must also focus on these.

2.2.1. Pre-market evaluation of efficacy – lack of data

In the pre-market phase, it might be (and certainly should be) considered essential to establish the safety and efficacy of a device before allowing it onto the healthcare market, enabling unrestricted use in patients. In order to make clinically sound decisions for their individual patients, clinicians need to evaluate how safe and effective a particular device is for treating a given condition in a group of patients similar to the patient that they are treating and how this compares to alternative devices and alternative therapeutic approaches (e.g. medical or conservative management).[73] The best study design to assess this so as to provide the least biased estimate is a blinded, randomised controlled trial (RCT) design recruiting patients who are representative of those for whom the device will be indicated. Additionally, it must compare the new device with current best clinical practice using appropriate clinical endpoints and sufficient sample size and duration of follow-up to detect clinically meaningful statistical differences in patient relevant outcomes.[74] However, for the most part this evidence is either missing or simply not available. This is particularly true at the point in time when devices first come onto the market, but it often remains true for many years afterwards.[30]

Hulstaert et al highlighted in 2012 that there is little clinical evidence needed to obtain the CE marking, the legal requirement for selling medical devices in the EU.[75] They explain that only evidence of safety and performance is required, even for many high-risk devices, and that this frequently did not necessitate clinical trials.[75] They also called for greater transparency, highlighting the fact that the evidence submitted for approval of CE marking is confidential and, therefore, is unavailable for scrutiny or for clinical decision-making.[75]

Whilst evidence must be provided by industry to the regulators to gain approval or permission to place their devices on the market, and to clinicians and healthcare payers (usually as unpublished data on case series or published studies in the literature) to gain access to the healthcare system, the quality of this evidence is often insufficient to determine the safety and efficacy of a device.[75,76]

Due to the lack of access to the data upon which approval for CE marking is based, Wild, Erdös, and Zechmeister drew on pre-reimbursement data as a proxy to assess the level of evidence available at the time of CE marking for cardiovascular devices, though reimbursement applications were being made between one to three years later.[77] They report that for most of the twenty-seven devices used for ten cardiovascular interventions[i] only low-level evidence, consisting of case series or small RCTs, was available when they entered the EU market. On further clinical investigation, four of these devices had safety concerns that prevented them from being marketed in the US, whilst only six had received FDA pre-market approval (PMA).[77] In fact, Hulstaert et al in reviewing the literature and examining dossiers submitted to the Belgian healthcare payer, RIZIV-INAMI, found that this is frequently the case for devices in Europe.[30]

It is often argued that it is not possible to generate the required evidence before market entry for a number of reasons, including the rapidity of the medical device lifecycle; issues related to the peculiarities of medical devices, such as the effect of learning curves on estimates of safety and effectiveness; or the difficulties in conducting the necessary rigorous study designs for medical devices that are required to demonstrate safety and clinical efficacy.[78–80]

However, these challenges are not insurmountable. For example, learning curves can be addressed within study designs through the careful selection of experts to conduct studies on the device.[81] Alternatively, learning effects may be incorporated in the analysis using statistical methods to adjust for them.[82] Sauerland et al have shown that it is entirely possible to conduct blinded RCTs if it is a requirement for reimbursement,[83] whilst Hulstaert et al point to alternative study designs that can be used to address issues such as small target populations and changing parameters using pragmatic trials and platform trials to include relevant comparators (and assessing clinically relevant study endpoints that matter to patients).[30] Yet there remains a dearth of clinically relevant data to determine the safety and efficacy of most medical devices entering the market.

2.2.2. Post-market evaluation of safety – lack of data

Even in the post-market phase there is a lack of availability of clinical data. Fraser et al argue that, whilst it is understandable that confidentiality be maintained during the approval process, nevertheless, the clinical data underpinning approval should be made available once the device has received CE marking, asserting that '*Clinically important results from the assessment of a medical device rarely equate with commercially sensitive data.*'[84] They also question the legality of the requirement for confidentiality of

[i] Reimbursement in Austria is not device-specific but intervention-specific.

clinical data referring to rulings made by the European Court of Justice on the right of access to clinical information related to the approval of medicines.[84]

Nevertheless, in the EU this data largely remains confidential, which Hulstaert et al, also found when they looked at the evidence base underpinning requests to the Belgian healthcare payer for reimbursement (and claiming that the device was novel, and adding clinical value) in 2019.[31] They assessed the assessor's reports[i] and found that all devices were invasive or implantable, and whilst 9/18 presented RCT evidence, it was mostly inappropriate or unsupportive (RCT on a different population, irrelevant comparator, surrogate outcomes, short follow-up, or outcomes unfavourable for the device). The evidence from their literature also supported this observation.

Improvements in the transparency of evidence have been promised, but delayed. A summary of safety and clinical performance (SSCP) is to be made available to the public for implantable and Class III devices, and updated annually, once the relevant software is in place. Additionally, there is a new procedure adding scrutiny to the clinical evaluation assessments conducted by notified bodies on manufacturers' clinical evaluations. This new scrutiny mechanism (CECP) means that an expert panel will review the clinical evaluation assessments and provide an opinion on the clinical evidence for all Class III implantable devices and Class IIb devices intended to administer/remove medicines from the body. Following these assessments the expert panel provides an opinion to the NB. These opinions are publicly available on the Commission's website. However, researchers from IQWiG, the German HTAB, recently investigated the contents of the CECPs published up to March 2023, to assess if the evidence base for high-risk medical devices was beginning to improve following the enactment of the MDR six years previously.[85] Yet, they found that the evidence presented in these reports was still of poor quality. There were seven devices subject to the CECP, only one had an RCT as supporting evidence for its use, for one of the claimed indications, and no supporting evidence for the other indications listed. Furthermore, the RCT had just forty-three patients enrolled for a follow-up of only four months. The other six presented evidence from non-comparative studies with 15-104 participants, and a follow-up of 4-24 months. All seven were high-risk implantable devices, three were cardiovascular implants. The CECP did not result in better evidence being generated, yet two of these devices are now on the market.

[i] The applications for funding submitted by manufacturers are confidential, so the only available evidence to assess their applications were the reports prepared on the applicants' devices by the assessor. These reports may be incomplete, since it is possible that assessors finding one reason for not agreeing to fund a device do not need to look further or need to write a comprehensive report detailing all the shortcomings of the application. This makes for poor data, but it was the best that is available given the legally imposed confidentiality on actors involved with assessing, regulating, and procuring these devices.

Furthermore, in the post-market phase it is often assumed that a device's short-term safety and efficacy have already been established. Where the effectiveness of a device has clearly not been established in the pre-market phase, and sometimes if a regulator requires it or a manufacturer perceives an advantage in it (e.g. to expand the indications, eligible population, or potential applications of the device), then post-market clinical studies may be performed. However, the Medical Device Directives (MDDs) lacked the authority to impose a requirement on manufacturers to conduct post-market clinical studies of devices, which has resulted in very few being published. However, even in the US, where the FDA has that authority, such studies are also scant and only published after several years of the device being in use. For example, Rathi et al investigated high risk therapeutic devices approved by the FDA in 2010/2011 and found that more than two thirds were required to conduct post-market approval studies, yet by 2014 less than a fifth of these had been completed.[86] This is too slow for clinical and policy decision-makers to make timely, informed decisions, and it is unclear whether the others will ever be completed.

Even if the short-term efficacy and safety have been established, there are still unknown risks and unanticipated adverse outcomes that may appear in the longer-term once a device is in use in addition to the uncertainty regarding longer-term beneficial effects. This necessitates a system of surveillance and vigilance in the post-market phase to detect changes in effectiveness and safety.

For the most part, surveillance and vigilance rely on voluntary reporting by users of the device of incidents and adverse outcomes to the manufacturer, the competent authority, or to an electronic incident reporting system. However, underreporting of adverse medical device events (AMDEs) is not uncommon.[25,87] In fact, it is the norm.

As evident in Table 2.1, authors found that there was significant underreporting of AMDEs to the relevant regulatory authority or online reporting system and several different approaches were used to identify the number of AMDEs and the number of devices used (i.e. the denominator required to estimate the rate). No single method identified all AMDEs.

Samore et al, using multiple approaches identified a 52-fold increase in AMDEs compared with the numbers of AMDEs reported,[25] whilst Hefflin et al identified a four-fold increase.[88] Craig, O'Meley, and Carter, found an approximately ten-fold difference in estimated AMDE rates compared with reported rates for urogenital mesh devices, and an approximately 250-fold difference for ventilators.[38]

Identifying the denominator was even more difficult, since there is no medical device register for recording individual devices (or even their aggregate number) being placed on the market or put into use, with the result that we don't know how many devices are

sold or used. Consequently, AMDEs are generally not reported as the rate per number of devices, but as a rate per number of admissions,[25,38,45,49] time period,[88] new CE marking,[46] unique device identifier (UDI),[47] or per user.[50]

Samore et al found that there was little overlap in the AMDEs detected by the different methods, and that passive surveillance reporting systems failed to pick up the majority of AMDEs, particularly for certain types of devices (e.g. joint implants). This illustrates the need for a multi-faceted approach to the detection of AMDEs to provide a more realistic assessment of the true rate of adverse outcomes related to medical devices.

Craig, O'Meley, and Carter described how the Health Issues Centre received 2,400 accounts of women's experiences of adverse effects during the period of the review of the Australian experience with urogynaecological mesh[i], though only 249 mesh-related AMDE reports had been submitted to the Australian Therapeutic Goods Administration (TGA).[38] It may be argued that implantable device failures may not be so obvious and or so readily detected, thereby, resulting in low report rates. However, as Craig, O'Meley, and Carter also demonstrate, even where incidents are obvious there can be significant underreporting.[38] In their incident review they estimated that less than 0.4 percent of ventilator failures were reported to the TGA, and that one in sixty-six patients could potentially be affected by a failed ventilator.[38] Ventilatory failure is an event that is obvious, meaning that detection of failure would be almost immediate, yet these events were not reported.

Perhaps of greater concern is the fact that vulnerable groups may be even more likely to experience harm than those who are less vulnerable. For example, Brady et al estimated that 3.3% of children admitted to one of 44 paediatric hospitals in the US experienced an AMDE, but those most affected were children aged less than two years.[45] Therefore, relying on PMS to identify poorly performing devices is unreliable since incident reports merely show the tip of the iceberg of all the unreported problems associated with medical devices.[89]

2.3. Improving medical device safety

Reason suggests that a pro-active approach to improving safety is required,[90] which requires identifying where the potential problems lie. Safety critical industries recognise that accidents and harm occur as a result of a series of lapses in judgement (errors) and that an incident occurs when these align, by allowing potential hazards, when they come together at the wrong time, to materialise into harm.[91,92] Reason describes this as being similar to a Swiss cheese.[92] He distinguishes between '*active failures*', which are

[i] Australian Inquiry by the Senate titled 'Number of Australian women who have had transvaginal mesh implants and related matters'

unsafe acts that occur at the '*sharp end*' of healthcare, and latent failures, which are decisions made more distally in a system that create the '*latent conditions*' resulting in '*resident pathogens*' in a system that predispose it to causing patient harm.[90, p.768-9] The results of active failures are more speedily observed, whilst the latent failures may not result in an incident for a much longer time, but they are the contextual predisposing factors that are identifiable and policy amenable, the removal of which reduces the risk of active failures leading to patient harm.

The Swiss Cheese model demonstrates the rationale for taking a systems approach to safety, and is used by high reliability organisations to ensure that the number of incidents is minimised.[92] A systems approach also aims to identify root causes and to avoid blaming individuals when the root cause is a systemic one.[93,94] In this way lessons can be learnt from incidents to improve safety and reduce the risk of incident recurrence. The same may be said of the medical device lifecycle with the different stages or processes that a device must undergo. If an error passes from one stage to another undetected or unimpeded the resultant medical device may be sub-standard and cause patient harm.

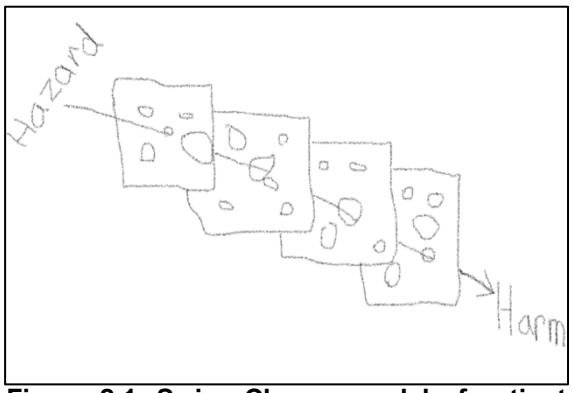


Figure 2.1. Swiss Cheese model of patient safety (adapted from Reason)[92 p.769]

Despite this, to date, there are few examples in the literature where the authors have taken a lifecycle approach to evaluating safety issues across the different stages of the life of a medical device.[28,95,96] Pane et al, coming primarily from an industry perspective present a bird's eye view of the different stages across the lifecycle discussing the 'safety issues' at different stages, comparing them with medicines, and making recommendations on how to address these issues.[95] In reality, they describe the requirements for safety data needed to obtain market approval. They do not describe the different processes involved. Furthermore, their recommendations mostly focus on improving safety issues in the post-market stages when the devices are in use, rather than in the pre-market stages when it may be possible to prevent harm. Besides, many of their suggestions have huge cost and system implications, mostly shifting the costs of data collection onto the healthcare system. Prevention would be better for patients, but prevention shifts the costs back to the developers and manufacturers.

Mytton et al describe the safety issues that become apparent across the technology lifecycle, but whilst they describe some of the key processes involved, they don't critique them or examine how they may be contributing to the problem.[96]

Focussing primarily on equipment and technology[i], Balka et al reviewed medical device-related safety issues, coming to the conclusion that determining their epidemiology was fraught with difficulty due to the lack of standardisation regarding the definition of medical device and AMDEs and their identification and reporting methods, together with reporting barriers that limit the hope of improvement.[28] Consequently, they argue that instead '*emphasis should be placed on understanding the underlying processes and use practices that come to bear on adverse events related to medical devices and technology*.'[28, p.S39] They present an overview of WHO guidance for regulating medical devices,[97] reflecting on particular issues, and emphasising the complexity of the problem of trying to determine hospital-based AMDEs. They conclude that medical device regulation debates should include a consideration of the need for data to support the understanding of AMDEs from a systems perspective.[28]

Others have assessed ways of improving medical device safety, often examining patient safety from a single perspective, usually the health care system perspective.[20,98,99] Consequently, many attempts have been made to improve clinical systems and reduce risks within the healthcare delivery context.[100–102] However, since medical devices are not confined to one system and most risks are introduced before the device enters the healthcare system, a multi-system or lifecycle approach is more appropriate.[62] This approach is required to identify errors across multiple systems that may align to admit an unsafe or ineffective device into healthcare that may result in patient harm, which is more likely to occur if these also align with errors in the healthcare system. Therefore, strategies need to be developed to safeguard against this. Indeed, WHO asserts that safety is everyone's responsibility and that all stakeholders should understand the processes involved in providing medical devices,[103] yet this is often not the case.

The WHO medical devices technical series seeks to address this gap by assessing how certain processes *should* be performed (e.g. procurement, HTA, regulation, etc.).[104–108] However, these descriptions are normative and are intended to improve the operation of these processes in low to middle income countries (LMICs). They assume that these processes are actually well conducted within developed or high-income countries and fit for purpose elsewhere. However, each of these processes varies across nations even within high-income countries. Furthermore, the focus of the WHO technical series is primarily on equipment, aids, appliances, and diagnostic devices. Implantable devices

[i] They use the definition provided in the MDD to define a medical device, but their article focusses primarily on equipment and technology, which appears to primarily mean information technology. Whilst they advocate taking a systems approach and consider 'governance' across the medical device lifecycle, their own focus is on AMDEs in the hospital setting, and how to better understand these. They are also interested in policy instruments used to improve patient safety, such as organisational policies, procurement, regulation, and HTA.

are not their focus, and these devices are sufficiently different in terms of their safety, risks, and follow-up mechanisms that the processes described in the guides are not so readily applicable to implantable devices.

Therefore, a multi-systems or lifecycle approach is needed to investigate the various systems, stages, and processes that introduce risks to implantable medical devices. Different disciplines, however, have different understandings of what the lifecycle means, with the lifecycle scope varying considerably, making it unclear what processes need to be examined most. For example, although both are intended for addressing risks across the medical device lifecycle, the WHO medical device lifecycle models used for guiding policymaking differs from that for guiding regulation.[108,109]

Other evaluation frameworks exist. For example, two promising lifecycle approaches are the IDEAL framework (Idea, Development, Exploration, Assessment, Long-term evaluation) and its derivative, the IDEAL-D, adapted for medical devices.[110–112] However, neither of these help to guide the assessment of risks and safeguards that may be introduced across the lifecycle. Indeed, there are a number of lifecycle evaluation approaches published in the literature, but, to the best of my knowledge, there is no review or synthesis of conceptual frameworks used to evaluate medical devices from a lifecycle perspective with a view to informing an exploration of how risks may be introduced during the life of a medical device (or examining how differences in meaning may affect patient safety). Therefore, a review of lifecycle models and frameworks used for evaluating medical devices was considered necessary to identify what stages and processes needed to be examined for policy-amenable risks to medical device safety.

2.4. Conclusion

The literature on medical device safety suggests that safety is a significant problem, but one about which we have little idea regarding its extent or its root causes due to the lack of available data. Reason argues that a systems approach is necessary to prevent harm,[91,92] whilst Ward and Clarkson have shown that error may be introduced across the life of a medical device.[62] This means that a multi-systems or lifecycle approach is needed to investigate causes of medical device harms.

Several researchers have explored medical-device related patient safety from a healthcare systems perspective, however, few authors have adopted a multi-system lifecycle approach for exploring causal or contributory factors of AMDEs. Balka et al did adopt this approach, but not in any depth, and not with implantable devices in mind.[28] They identified many challenges in conducting research into medical devices and concluded that greater recognition of the need for better data was required and that

taking a systems approach to medical device governance is necessary to address the evidence gap.[28]

3. Methodology

Taylor and Francis distinguish the concepts 'methodologies', 'methods', and 'processes', by explaining that methodologies are "particular sets of theoretical assumptions, which underlie the choice of data collection and analysis methods and processes", whilst "methods are *what* you do to collect and analyse data, and processes are *how* you go about doing them."[113 p.3, italics in original] This chapter describes my research methodology. It makes explicit my assumptions (as far as I was aware of them) when I began the research[i]. I had some deeply held assumptions – I assumed that a lack of knowledge is a remediable cause of unsafe medical devices reaching patients and that patient safety matters to everyone. I also assumed that the purpose of regulating medical devices is to protect patients[ii].

Creswell and Creswell suggest that there are three broad types of research methodology with different underlying philosophical assumptions, namely qualitative, quantitative, and mixed-methods.[114]

- *'Qualitative research* is an approach for exploring and understanding the meaning individuals and groups ascribe to a social or human problem.'
- *'Quantitative research* is an approach for testing objective **theories** by examining the relationship among variables.'
- *'Mixed methods research* is an approach to inquiry involving collecting both quantitative and qualitative data, integrating the two forms of data, and using distinct designs that may involve philosophical assumptions and theoretical frameworks.'[114 p.4, bold and italics in original]

As the research is exploratory in nature, I adopted a qualitative methodology[iii]. The rationale for using a qualitative methodology, and its advantages and limitations are described in section 3.1. I will try to explain my philosophical assumptions in section 3.2 on positionality, the theory underpinning the research in Section 3.3, and the conceptual framework guiding the overall research project in section 3.4. The thesis research strategy is explained in section 3.5.

3.1. Rationale for using a qualitative methodology

Strauss and Corbin assert that a qualitative approach is useful for trying *'to understand the meaning or nature of a* problem', and for exploring *'substantive areas about which*

[i] In fact, assumptions are often deeply held beliefs, whose existence we often only become aware of when they are challenged in some way.

[ii] All three of these particular assumptions have been challenged by my findings!

[iii] Although, mixed-methods research is also appropriate, and that is what I had hoped to do, as it can provide a deeper understanding of a phenomenon and its context. However, this wasn't feasible due to the lack of available (or gatherable) quantitative data on medical devices.

little is known or about which much is known to gain novel understandings'.[115] This research sought to gain a detailed and novel understanding into the nature of the medical device lifecycle, and its key processes, in order to understand how they contribute to patient safety and harm, making a qualitative approach appropriate. Furthermore, I consider the issue of medical device safety to be a matter of social justice, and for this Creswell and Creswell suggest that *'a qualitative approach is typically best'.*[116 p.20]

3.1.1. Advantages of qualitative research

Compared with quantitative research methods, which are best for answering questions that can be answered through quantification, qualitative methods are more useful for exploratory research, to develop hypotheses, and to explain why hypotheses might be true or not.[74,117]

Despite previous arguments in the literature about the value of qualitative research, it is widely recognised that qualitative research methods are useful for exploring a phenomenon in depth, exploring meanings that people attach to lived experiences, gaining an understanding of how processes work, and for explaining why some interventions work in some places for some people but not in others.[118–121] These are important areas of research for which quantitative methods are ill-equipped, whilst qualitative research can '*reach the parts that others cannot'*.[122]

Additionally, Rogers suggests that qualitative research methods are appropriate for exploring processes, as they can be used to determine '*the sequence of events over time'* and '*to gain insight and understanding of human behaviour*',.[123 p.196]

Another advantage of qualitative research is that it is not rigid in its approach, thereby allowing the researcher to shift focus as data collection and analysis progress, enabling an emergent research design that is responsive to the findings.[124 p.351] This was a particular advantage for this research topic as the intention was to start with a broad overview of the lifecycle to identify the key processes and key concerns, and then to narrow the research as it became clearer where to focus in greater depth, based on emergent findings suggesting where the greatest risks or opportunities for policy intervention lay.

Therefore, for all these reasons, a qualitative research methodology was considered the most appropriate methodology for exploring the medical device lifecycle, its processes, and associated risks to patient safety.

3.1.2. Limitations of qualitative research

Whilst it is valuable, qualitative research does have some limitations. For example, the validity of qualitative research may be questioned. However, qualitative researchers argue that what matters is the trustworthiness of the study's methods and findings, and

suggest a number of research strategies to ensure trustworthiness, such as, providing access to data, and creating an audit trail. Therefore, these and other strategies have been used in this study to ensure the trustworthiness of the research.

Another limitation of qualitative research is its lack of generalisability, although qualitative researchers argue that whilst not generalisable in the statistical sense, nevertheless, findings may be generalisable to the phenomenon, providing transferable learning.[125,126] I would also argue that generalisability is often not the point of qualitative research, and that findings which are only true for a particular context still provide worthwhile knowledge about that context. Certainly, whilst the findings of this research may provide transferable learning regarding the regulation of other products, I think that medical device safety is sufficiently important that providing insights with the potential to improve patient safety should be a worthwhile contribution in its own right, making transferability of the findings to other contexts, perhaps, less important than its truth value.[126]

3.2. Positionality

Taylor and Francis link the underlying theoretical assumptions to a researcher's worldview, explaining that the researcher's philosophy determines the choice of research methodology.[113] Therefore this section describes my philosophy and the influence this has had on the research.

All data, and indeed all research, is subject to interpretation. Interpretation is the process of making sense of the data, whether it is quantitative or qualitative, and is greatly influenced by the researcher's stance or position as these form the lens through which we see, understand, and report a phenomenon.[127–129] The concept of positionality also has a second meaning, that is where the researcher is situated in relation to the research in terms of the subject matter and, in the case of interviews, the data subjects, which also influences the researcher's interpretation of the data. I will now explain both of these (starting with my situation and then explaining my stance), so that readers may better understand why I approached the research in the way I did, how I interpreted the data, and the biases inherent in my interpretation.

3.2.1. Situation

I am a medical doctor with training in conducting Health Technology Assessment (HTA). Working in the healthcare service, both as a doctor and as an HTA researcher, has given me unique insights into how medical devices are perceived, procured, and managed. It has also given me access to information, and to stakeholders, that I might not otherwise have had access to. The result is that, based on my past HTA research projects, I started

this research with the impression that medical devices have little evidence to support claims that they are effective and safe.[130–132]

Integral to the practice of medicine is the belief that '*suffering can be ameliorated*' and '*the value of a common social good,*'[133, p.175], balanced against an acceptance that healthcare carries risk, and that those risks have to be weighed against the likely benefits of treatment, taking into account the severity of the patient's condition, the alternative treatment options, and their likely prognosis with and without treatment. This requires an understanding of what the risks and benefits are for each treatment option.

Talking with clinicians, it became apparent to me that they don't understand how medical devices are regulated. They assumed that the CE marking means that devices have been proven to be safe and effective before being allowed onto the market (but it does not mean this[i]), and as a result have made decisions based on a misunderstanding. Consequently, this misunderstanding of the CE marking may result in Procurement buying, or clinicians choosing to use, an unproven and sub-standard device that may lead to patient harm. The development of my thesis conceptual framework was directly influenced by this realization that the lack of understanding of the regulatory process can have an adverse impact on patients' outcomes due to incorrect assumptions.

3.2.2. Stance

As a medical doctor I come from a primarily positivist tradition that seeks cause and effect analyses of illness and therapies in order to determine the most effective treatment for a given illness. Whilst I also appreciate that we construct our understanding and appreciation of reality through experience and our interpretation of those experiences, nevertheless, I have been heavily influenced by the positivist and post-positivist framing of reality. Furthermore, I take a pragmatic perspective, and I agree with the systems stance to patient safety, that it is better to understand what has gone wrong in order to seek to prevent it from happening again, rather than as an exercise in attributing blame.[92,134,135] Consequently, I try to be fair and avoid blaming.

This means that I operate, as far as possible, from an objective stance, and I try to be as objective as possible in gathering and analysing data, constantly looking for evidence both for and against any supposition or hypothesis and keeping an open mind, whilst seeking the truth. Taking a neutral and objective stance is an essential requirement for analysing quantitative data so that the research findings and conclusions are valid representations of the truth. However, qualitative data analysis requires taking a more personal or subjective position.

[i] As will be shown later, CE marking does not mean that a device has been proven to be safe and effective, though this is a common perception.

All research is interpretive, it involves making judgements, but the rules for making those judgements are largely unspecified for qualitative research[i]. This contrasts with quantitative research where, for example, there are guidelines for ascribing causality[ii], or for conducting and interpreting statistical analyses[iii], requiring a neutral and objective approach to data interpretation. In contrast, interpretation of qualitative data, whilst it must be evidence-based, cannot be neutral, it requires taking a stance as this is the researcher's tool for analysis. It is the lens through which they evaluate and interpret their data. Qualitative researchers must decide what they think the data says and own that opinion.

Whilst I take a pragmatic worldview generally, the stance that I have taken to analyse my data in this study is a critical interpretive one, because I consider patient safety to be a matter of justice and that where there is an injustice this should be remedied. Regarding regulation, my stance is that medical device regulation should protect patients, not least, because most people believe that it does.

3.3. Theoretical Underpinnings

Theory played an integral role in the design and execution of this research, from the development of the conceptual framework based on what I thought was going on, to the use of theory to design studies, analyse data, and synthesise findings into a coherent whole.

Focussing on patient safety, I examined reports regarding how patients are harmed and theories related to accident or incident prevention generally. Reason explains that incidents occur as a result of failures or errors in decision-making, but that these are rarely single errors, but rather a series of errors within a system.[91,92] His 'Swiss Cheese' theory of incident occurrence illustrates how failures or errors in decision-making within a system, such as the healthcare system, may occur yet not result in harm, though they introduce hazards at various points in time or place. Harm occurs when a series of failures (errors in decision-making) result in the aligning of hazards or hazardous situations (or sequences of events) that allow the latent failures (hazards introduced

[i] I do not mean that the methods are unspecified, but that having carried out the research processes according to the specified methods it is then necessary to interpret the analysed data to create a synthesis that takes a position on the topic. To paint a picture requires choosing colours, a stance may be likened to that choice, since the colours we choose create the picture, providing it with atmosphere and conveying emotion. Similarly, of all the patterns in the data, which way do we arrange them into themes, and from all those themes, which do we choose to present as findings. A guiding principle is to choose those that are relevant to the research question and to the objective of the study, but how and what we 'see' as a finding's relevance depends on our particular perspective.

[ii] The Bradford Hill criteria.[136 p.374-79]

[iii] For example, using p-values to assess the probability of whether an observation is due to an intervention or due to chance.

more distally) to materialise as actual harm following an error at the 'sharp-end' of decision-making, for example, when the surgeon chooses which device to implant.
In his theory on the diffusion of innovations[i], Rogers explores the factors that influence diffusion,[137] including the attributes of the innovation, the adopter, the communication (message) and channel (communication medium), and the social context, as well as the decision to adopt[ii]. From this theory he derived the innovation-decision model, which, as can be seen from Figure 3.2, is very similar to my conceptual framework, shown in Figure 3.3, providing greater theoretical support to my conceptualisation of the problem and highlighting some key issues that later emerged as factors affecting patient safety, particularly communication. I also found it useful for examining and comparing lifecycle models, providing key insights into the forces at play, particularly during the diffusion phase of the lifecycle.

The next section describes how the issue of medical device safety was conceptualised and how this led to the overall design of the research.

3.4. Conceptual framework

Theory underpins how we approach a research question.[138] A theoretical or conceptual framework guides the research by defining the perspective and scope of the research

[i] which I found to have profound influence across the life of a medical device.
[ii] Rogers conceptualises the lifecycle of an innovation in terms of its level of uptake (i.e. its diffusion) and asserts that 'innovations do not sell themselves', consequently the life of an innovation is influenced by a number of factors, including the innovation itself, the agents or actors involved in 'selling it', their communication processes or channels, the social system (context) and the timing.[137]
He describes the decision to adopt an innovation, the 'innovation-decision process', as progressing through five stages: knowledge, persuasion, decision, implementation, and confirmation, suggesting that the success of an innovation depends on it following this sequence of stages in the innovation-decision process.
According to Rogers, the innovation is characterised in terms of its relative advantage, compatibility (with social norms and values), complexity (perceived ease of use), trialability and observability. Additionally, an innovation is not necessarily a static thing but may be reinvented or developed as its adoption diffuses.
The actors involved may be 'change agents' who deliberately aim to improve the diffusion of an innovation, or peers of the proposed target group to whom the innovation is being proposed for adoption. Peers may seek to deliberately increase the adoption of an innovation, but more often they influence each other unintentionally by virtue of having some shared context, values, or connections with others, and by providing a point of reference for them regarding the usefulness, potential advantages, usability, and experience of an innovation. Rogers subdivides potential adopters of the innovation into five categories, calling them innovators, early adopters, early majority, late majority, and laggards, based on their propensity to adopt it quickly or slowly as evidenced by their timing of initial adoption of the innovation. Communication channels may be considered as a means of connecting two individuals, this may be face-to-face, via mass media or other means. Communication is more likely to be effective between two people if they share a common culture with the accompanying values, norms and a shared understanding of meanings.
Rogers explores each of these influences and their effects on the success or failure of an innovation, demonstrating how these particular features can explain why one innovation spread rapidly when another (though it might be similar) failed.

problem, identifying the concepts and variables to be examined, providing a general research approach to examining the research questions, and prescribing the research methods that are possible or appropriate to addressing those questions.[139] I initially constructed my conceptual framework by drawing on my own experiences and understanding of factors that might impact decision-making combined with theories of patient safety. It was further refined as the research progressed.

The notion of errors in decision-making resulting in latent failures within a system is the central concept of my conceptual framework. If errors or other failures in decision-making during the various lifecycle processes can introduce hazards that may result in patient harm, then identifying those errors (or hazards), and the factors influencing them, become key policy intervention points with a high potential for improving patient safety. Figure 3.1 illustrates this as a simple logic model.

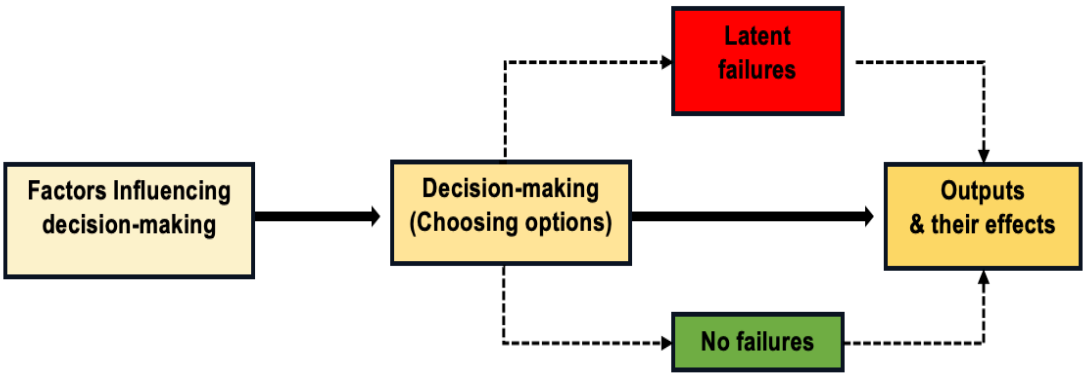


Figure 3.1. Simple logic model of the effects of errors in decision-making

As I understood it, the factors influencing decision-making included *Knowledge*, *Understanding*, *Experience* (including training and skills), *Attitude* (including values), and rules governing our decisions, such as protocols, standard operating procedures, guidelines, behavioural norms, and regulation, which I have called '*Decision-making rules*'. Expanding my logic model to incorporate these factors, I conceptualised the effects of the decision-making process as a sequence of steps leading to the outputs from any given process or sub-process.

To take into account that this is assumed to occur for each of the lifecycle processes, I added a high-level representation of what I considered at the outset to be the key processes in the life of a medical device, combining them to create the overarching thesis conceptual framework guiding my original choice of research topics and questions, shown in Figure 3.3 and explained in the next sub-section.

The assumptions underpinning my conceptual framework are set out in Box 3.1.

Premises and assumptions underpinning my initial conceptual framework:

- Patient safety depends on good decisions being taken to prevent risks across the entire life of a medical device.
- Patient harm occurs not as a result of one poor decision, but as a result of a sequence of events, where a hazard that could have been avoided or minimised at some stage in the lifecycle was missed, and that safeguards during subsequent stages of the lifecycle didn't prevent the potential hazard from progressing nor the harm from materialising (The Swiss cheese model).[92]
- Each process has its own set of actors, who make decisions regarding the conduct of their part in the lifecycle.
- Decision-making at each stage in the lifecycle is influenced by a number of factors, including the level of knowledge of key actors and their understanding, not only of their own process, but also how the other lifecycle processes operate, and their inputs, outputs and risks to patient safety.
- Other factors influencing decision-making include the attitude and experience of actors, and 'decision-making rules', such as norms, standards, guidelines, and legal requirements.
- There is a lack of data about process outputs, including patient outcomes, which results in a knowledge gap.
- Lack of knowledge results in assumptions being made, potentially affecting key decisions that may, ultimately, jeopardise patient safety.[140]

Box 3.1: Summary of premises upon which the initial conceptual framework was constructed

3.4.1. Description of my conceptual framework

The conceptual framework in Figure 3.3 illustrates my conceptualisation of the problem. It embodies the factors that I assumed were involved in introducing hazards to patient safety into the medical device lifecycle.

Based on my own experiences with different actors, it seemed likely, due to the numerous processes and disciplines involved, that actors from one lifecycle stage might not understand how other lifecycle stages function and, in the absence of the necessary knowledge and understanding, they make assumptions, so that latent failures or weaknesses in one part of the lifecycle may not be recognised or addressed in other parts of the lifecycle.[92] I assumed that misinformed decisions based on erroneous assumptions introduce latent failures that could eventually materialise as patient harm. For example, in the belief that the safety and effectiveness of a medical device has been tested in an RCT before being allowed onto the market, a surgeon may assume that devices on the market are safe and effective, whereas in fact, many devices on the

market have never undergone a clinical trial, let alone an RCT.[1,141] Conversely, a medical device manufacturer may assume that surgeons systematically report all instances of adverse outcomes related to their product, and as such, having received few or no reports, may assume that there are very few incidents associated with the device, when in fact many incidents are not reported at all.[25,38]

Clearly other factors may also influence decision-making, such as attitude and experience[i], together with the previously mentioned 'rules' governing decisions.

I also assumed that feedback of information gleaned about the outputs from a given process and the resultant patient outcomes would influence future decision-making, because in an ideal world the outcomes *should* result in learning (knowledge), and I assumed that better knowledge would result in better process outputs that should eventually improve patient outcomes.

Drawing on Reason's Swiss Cheese Model of system failure described earlier,[92] I conceptualised the 'system' as the medical device lifecycle, with each stage having its own hazards and safeguards. When the safeguards in one or more stages fail and hazards across the stages align, they allow the risk to pass through, causing patient harm. This model assumes that there is a decision-making process at each stage of the lifecycle that is subject to these influences, and although the decision being made and the outputs from each process differ, the influencing factors are similar and each process ultimately contributes to patients' outcomes.

[i] For example, attitudes to safety and whether safety features as a consideration or a concern or not; experiences with their own process, which may increase their skill or cause them to take shortcuts or workarounds circumventing quality controls; professional or personal experiences of adverse medical device outcomes, which might heighten their sensitivity to risks and patient safety.

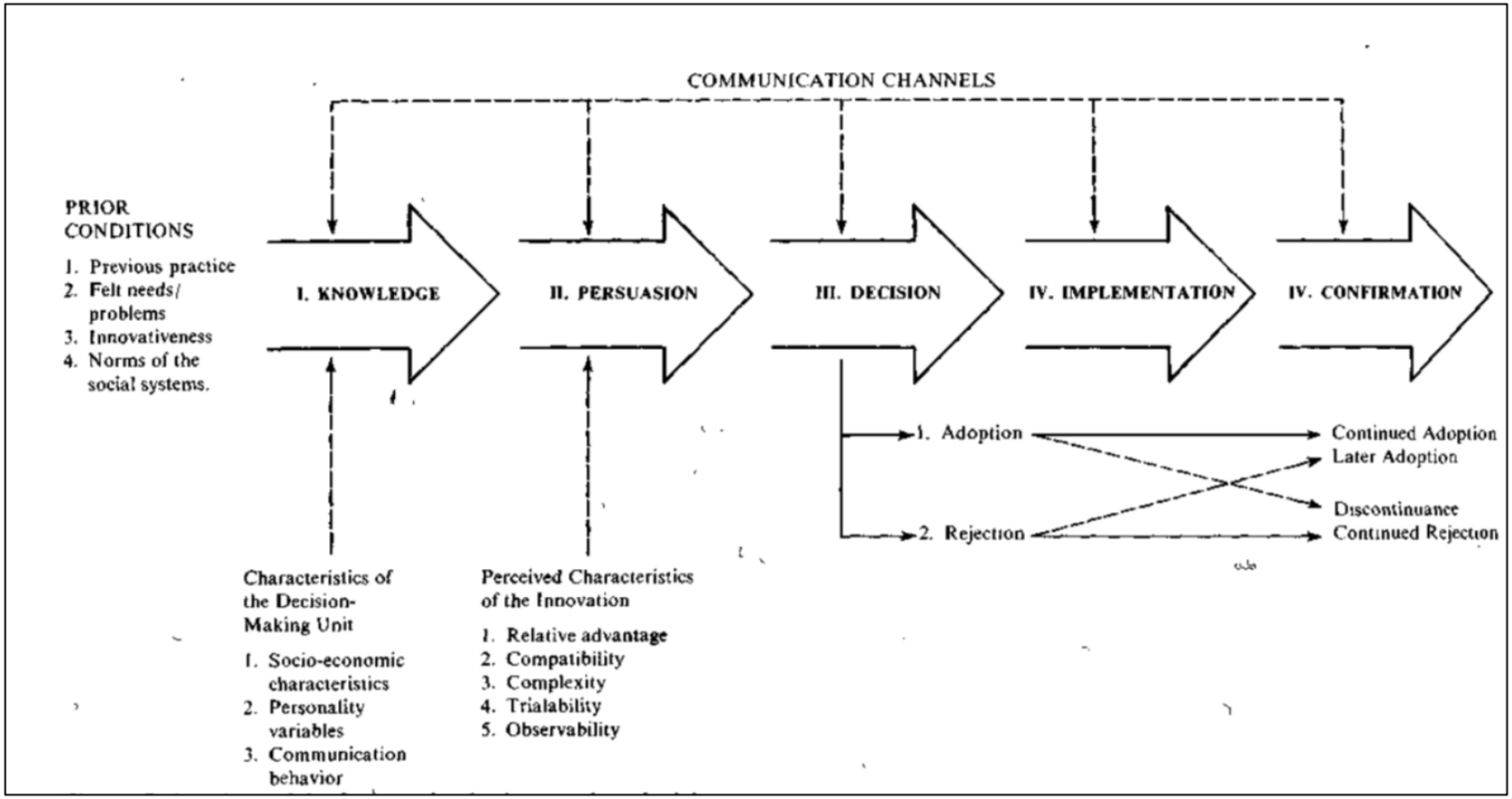


Figure 3.2. Rogers' model of stages in the innovation-decision process[137]

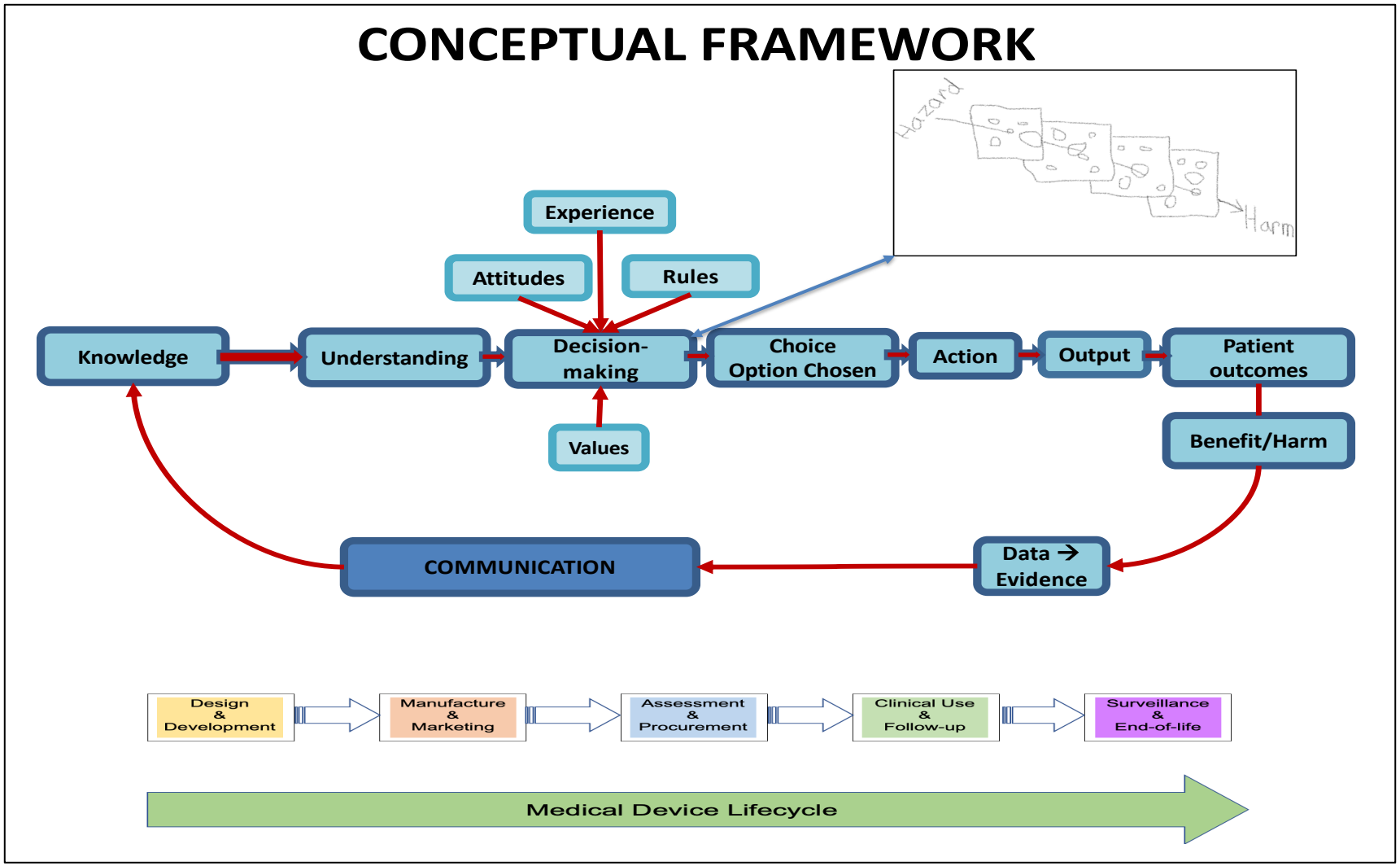


Figure 3.3. My Conceptual Framework

3.5. Research Strategy

The overall question that I sought to answer through my research was:

What are the policy-amenable factors impacting patient safety, and potential solutions, across the medical device lifecycle?

3.5.1. Developing the research approach

To achieve this, I considered it necessary to:

- Identify the phases, stages, and processes involved that are conducted across the life of a medical device.
- Explore the key lifecycle processes to understand how they are operated, how they introduce hazards and risks (to patient safety), their existing safeguards, and what other safeguards might be put in place to protect patients from unsafe or ineffective medical devices.
- Explore the regulation of medical devices to understand how medical devices are regulated in the European Union (EU) and how this affects their safety.

However, as the research progressed it became clear that it was unreasonable to expect everyone to understand all the processes, and it shouldn't be necessary for all stakeholders to know everything that happens across the medical device lifecycle to ensure that a device is safe and effective. Furthermore, whilst many of the hazards resulting in patients being harmed are introduced during the design and manufacturing phases, it is the regulatory process that is the most significant process in terms of being able to safeguard patients from unsafe and ineffective devices. Yet prolonged engagement with the lifecycle models, and an international placement examining what evidence is available when devices are permitted to enter the market, suggest that the regulatory process does not adequately safeguard patients, which made me question why not. This resulted in a change of focus, with a more in-depth examination of the regulatory process[i], and an expanded and prolonged analysis of the lifecycle models.

However, exploring the regulatory process required additional conceptual frameworks to guide what to explore and how to explore it. To identify these, I reviewed the theoretical literature on regulation. The multiple definitions of regulation described by Baldwin, Cave, and Lodge provided a multi-level conceptualisation of regulation that framed the research.[142, p.3] Nested within this, I used Coglianese's programme theory of the regulatory process as a conceptual framework to explore how the EU regulates medical devices.[143] I drew on Coglianese's description of the core components of regulation,[144]

[i] Additionally, there is a wealth of legislative history and other policy documents that are publicly available to draw on, providing a rich source of data useful for generating an in-depth understanding of this process.

and Stigler's Public versus Private Interest theory of regulation,[145] as an analytic framework. This is illustrated in Figure 3.4. The theories of regulation require more in-depth explanation, therefore they are the subject of the next chapter.

Figure 3.5 shows the ultimate research logic model, whilst Table 3.1 provides an overview of the ultimate research design. Appendix 14.2. provides a summary linking the research questions to the methods.

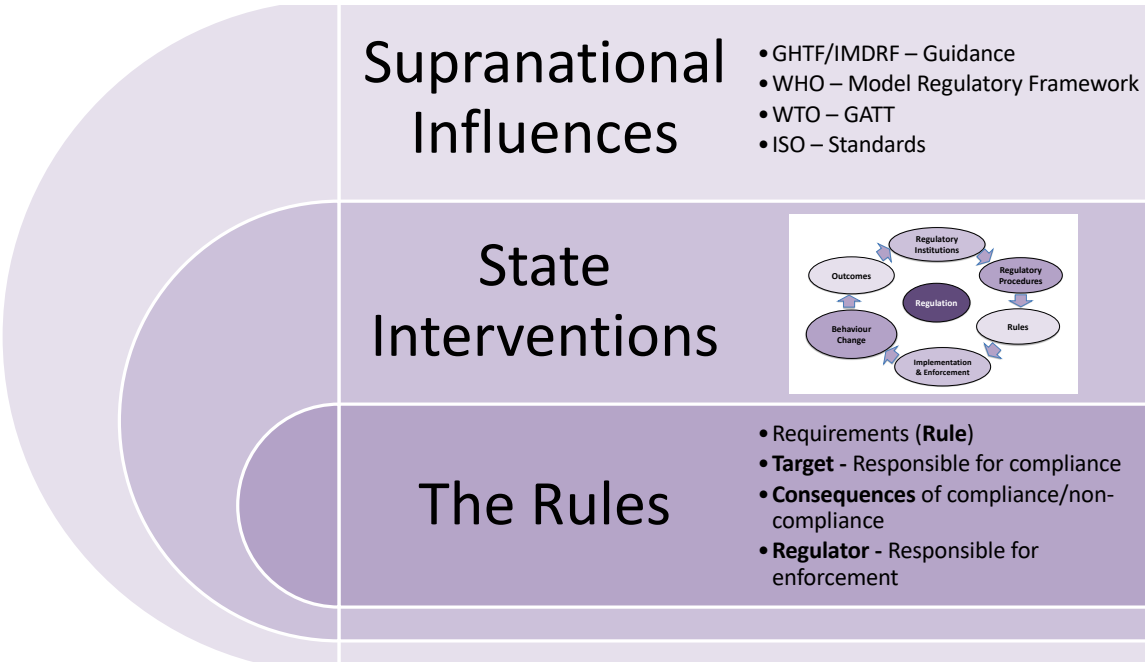


Figure 3.4. A multi-level conceptual framework of medical device regulation

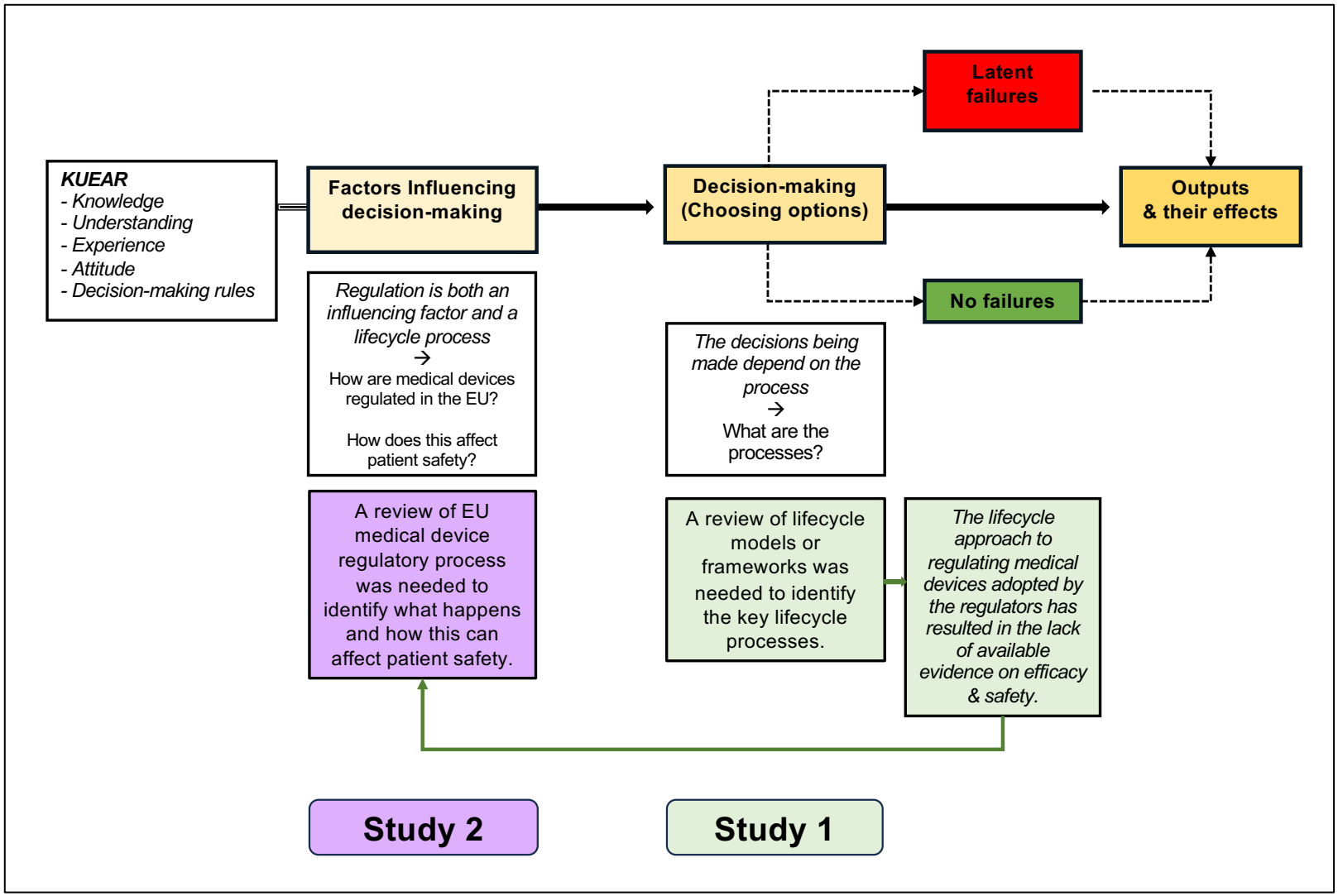


Figure 3.5. Research logic model

Table 3.1. Summary of research design

Study	Lifecycle Review	Regulation Review
Research Question(s)	What lifecycle approaches, models or frameworks have been used to evaluate medical devices? What is meant by the 'medical device lifecycle' and 'lifecycle evaluation'? How do these differences in meanings affect patient safety?	How are medical devices regulated in the EU? How does this affect patient safety?
Data source(s)	Literature; Grey literature; Documents.	Legislation; Guidelines; Standards; Reports; Web pages; media representations; Regulation-related industry webinars.
Study Design	Qualitative (evidence) synthesis (literature review)	Qualitative document analysis
Analysis	Data extraction – coding & categorisation, comparing categories across perspectives; Narrative descriptions & historical summaries; Model representations – transforming these from one format to another to identify similarities & differences; Writing.	Narrative summaries; Historiography & historical timelines; Tracing legislative history; Narrative summaries of actor groups & processes; Diagramming legal procedures & timelines; Juxtaposing timelines & events; MDD & MDR – coding & categorisation (Regulatory target, rule, requirements, conditions, triggers) & comparison across actor groups, and extracting data according to identified themes for comparison.
Synthesis	Qualitative Synthesis – Comparative Analysis; Model typology; Thematic Analysis.	Historical narrative; Qualitative description; Interpretive description; Thematic analysis; some descriptive statistics.

4. Theory of Regulation

4.1. Introduction

This chapter reviews theories of regulation to provide a theory-based understanding of what regulation is, how it is defined, and how it works. Drawing on the relevant literature, I define the concept of regulation, explain the potential reasons for introducing regulation, describe the different ways and means of regulating (including the core regulatory components), and present a theoretical understanding of how regulation works in practice. The chapter provides the theoretical background and the rationale for the methods and analytical approaches used for exploring the medical device regulatory framework presented in Chapter 8.

4.2. What is meant by regulation?

Regulation may be considered to be a process or mechanism that directs or alters the outcomes of a dynamic system, which is underpinned by a set of governing principles or rules. From this perspective, regulation may be a natural process, similar to the mechanism for achieving homeostasis or homeorhesis[i] in a biological system; or it may be a deliberate intervention by an entity or entities to influence the outcome of a process. Leaving natural processes aside and focussing on the regulation of human activities or behaviour, Baldwin, Cave and Lodge suggest that it is helpful to think of regulation in one of the three ways (see Box 4.1).[142, p.3]

Definitions of Regulation
1. ‘As a specific set of commands—where regulation involves the promulgation of a binding set of rules to be applied by a body devoted to this purpose.’ 2. ‘As deliberate state influence—where regulation has a more broad sense and covers all state actions that are designed to influence business or social behaviour.’ 3. ‘As all forms of social or economic influence—where all mechanisms affecting behaviour—whether these be state-based or from other sources (e.g. markets)—are deemed regulatory.’[142, p.3]

Box 4.1. Three definitions of regulation from Baldwin, Cave & Lodge

[i] ‘Homeorhesis, derived from the Greek for "similar flow", is a concept encompassing dynamical systems which return to a trajectory, as opposed to systems which return to a particular state, which is termed homeostasis.’ [Internet]. Accessed 2020 Apr 26. Available from: https://en.wikipedia.org/wiki/Homeorhesis

The **set of rules** used to regulate an entity include legislation and any ancillary rules that supplement the legislation, such as relevant guidelines, recommendations, 'regulations', technical standards, standard operating procedures (SOPs) and manuals.

State interventions include all mechanisms of regulation at a state's disposal (not just the establishment of rules or legislation), including choosing not to intervene.

The **third definition** constitutes all regulatory mechanisms that are beyond the state's deliberate actions to influence a particular behaviour. This includes State socio-economic policies directed at other sectors that have an effect on the behaviour of interest; all deliberate actions or activities by regional, international or supranational bodies aiming to influence the specific behaviour or interest; and all unintentional supranational or international influences (e.g. actions taken in other policy spheres, for example the Free Trade Agreements of the European Economic Area (EEA)) and events, such as natural or man-made disasters (e.g. pandemics, earthquakes, wars, economic crashes, and so on) that also affect the specific behaviour of interest.[146].

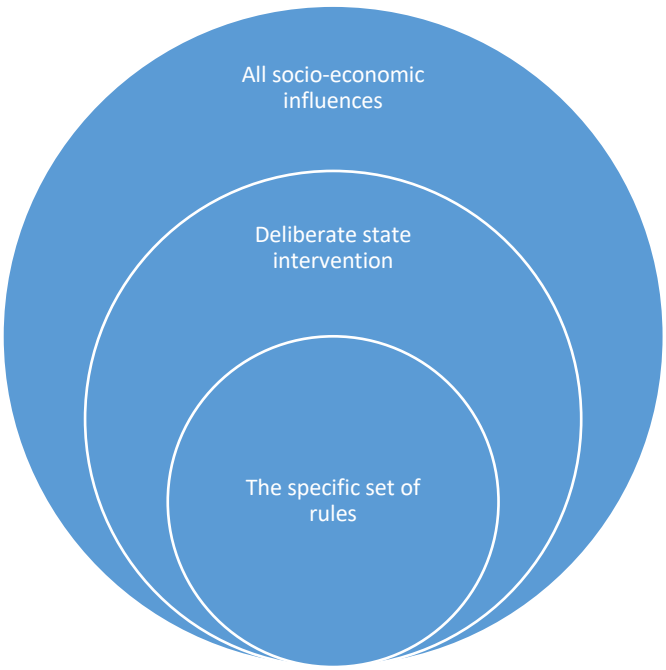


Figure 4.1. Three definitions of regulation (by Baldwin, Cage, and Lodge)[142, p.3]

Thus, the ways in which regulation can be conceptualised are diverse, ranging from a broad perspective encompassing all factors and mechanisms that influence behaviour (whether intentional or unintentional, including influences or interventions at a supranational level), or more narrowly referring to all forms of deliberate intervention at the disposal of an individual government to influence behaviour, to the most narrow definition which limits the concept of regulation to a specific rule, norm, or set of rules (usually introduced by a government) aimed at influencing the behaviour of a specific group or entity.

However, it is clear that the aim of deliberate regulation is to alter specific behaviours, the goal of which is to influence the outcome of some activity. It is also clear that there are three levels at which intervention may be introduced (and a fourth level of influence that arises from unintentional influences): at the level of the specific rules themselves (The Rules); at the level of the State (State Interventions); or at a more regional or global level (Supranational Interventions) as represented in Figure 4.2. These levels represent the multiple layers of context within which a regulatory process, such as the regulation of medical devices, operates. Each level represents a layer or sphere of influence, with the innermost sphere perhaps exerting the most immediate influence on the process, but not in isolation from the influences arising from the outer two levels. Therefore, the review of the regulatory framework for medical devices in the next chapter will address all three levels of intervention but with varying degrees of detail[i], with its main focus on an in-depth analysis of the rules set out in the EU.

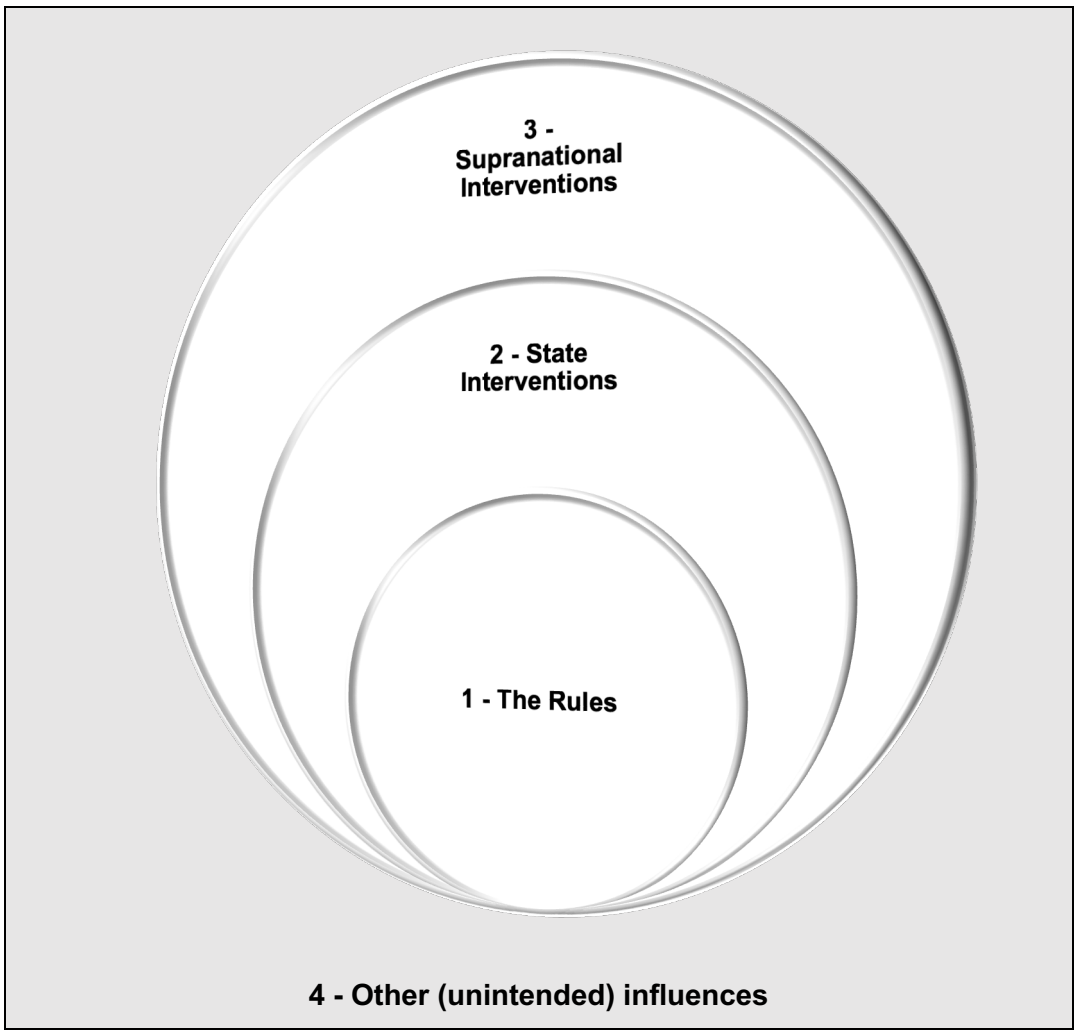


Figure 4.2. Levels of Regulation

[i] In particular, and to limit the research scope, non-intentional influences are not examined in any detail as they are likely to be less amenable to policy intervention.

Before examining how the regulatory process works, it is worth reflecting on why governments (or others) regulate anything in the first place, what are the available means for regulating, and why regulate medical devices in particular. I present some of the underlying theories on regulation below.

4.3. Why regulate?

According to den Hertog, there are two prevailing theories as to why governments regulate: The first is the ***'public interest'* theory of regulation**, which suggests that regulation is put in place to promote or increase social good or public welfare; and the second is a ***'private interest'* theory of regulation**, which suggests that regulation is put in place to promote the welfare of specific interest groups, such as specific industries.[147] Each theory has different underlying assumptions.

The *public interest* theory assumes that regulators have 'perfect information', (or sufficient at least) to make informed choices; have the power to enforce rules; are benevolent; aim to pursue public welfare or interests; that there exists a 'market failure'; and that government intervention is effective in addressing the market failure.[147]

Private interest theory assumes that regulators are imperfectly informed or have insufficient information; do not have sufficient power to enforce rules; and that all economic operators pursue their own interests.[147] These theories will now be discussed in more detail.

4.3.1. Public Interest Theory, Markets and Market Failure

According to the neoclassical tradition of economics, a *'market'* is defined as a means of allocating scarce resources that is a mechanism of adjustment between the supply and demand of a particular good or service based on price and quantity signals conveyed between producers and consumers, without government intervention.[148]

The assumption is that consumers will buy as much as they want of a particular good or service at a given price to maximise their utility and producers will sell as much as they can at a given price (whilst balancing this against the costs of production) to maximise their profit, and that the supply and demand of a particular good achieves balance (equilibrium) at the price and quantity that best suits the needs of both parties. In other words, consumers' demands will change according to the price, and the quantity offered for sale by producers will also change according to the price, so that at a certain optimum price the quantity or amount being offered for sale will equal the amount being bought by consumers. At this point of equilibrium, where all products offered by the producer are sold and consumers want no more at that price, the market is said to be 'cleared'. Furthermore, since the market is responsive to the price of the good being offered for

sale, those producers who can lower their costs of production can offer the good at lower prices which will result in them competing successfully against less efficient producers who have to either lower their costs of production (increase efficiency) or leave the market. Thus, according to the theory of perfect competition, only the most efficient producers remain in the market. These equilibrating mechanisms are considered by economists to be how, in ideal circumstances, markets work.

When the theory holds true then pricing can be used as an efficient mechanism for allocating scarce resources, and this is the justification for promoting competition in a market. However, like all theories, it is based on a number of assumptions (see Table 4.1.). However, it isn't always necessary to perfectly fulfil every assumption for a given theory to work reasonably well, but some assumptions are crucial and, in this case, when the crucial assumptions do not hold true it results in *'market failure'*, that is to say that the market mechanism then fails to achieve the optimum allocation of resources.

Table 4.1. Assumptions underlying the theory of perfect competition

The Theory of perfect competition assumes that:

1) Producers are competing
2) All producers seek to maximise their profits
3) Each producer is so small that they cannot individually influence the price or control the market
4) Consumers are fully informed (perfect information)
5) Consumers possess the ability to seek out the producer with the best price
6) Consumers are the best judges of their own needs, wants, desires, and well-being
7) All other things remain constant, such as consumer tastes, incomes and the prices of other goods
8) The increased cost of each extra unit produced is less than the extra revenue received
9) The market clears where demand is equal to supply
10) Consumers make rational choices.[148]

Donaldson and Gerard argue that the perfect market system is one which would unequivocally work best for healthcare **IF** the ideal conditions of the perfect market were met, because, under ideal conditions, the perfect market would result in maximum consumer satisfaction (utility), that is, the greatest amount of 'well-being' for patients and the public that is possible within the resources available to society.[148] They suggest that the crucial assumptions that must be met for the theory of perfect competition to work for healthcare are that:

i. There is certainty
ii. There are no externalities

iii. Consumers and producers have perfect knowledge
iv. Consumers act free of self-interested advice from doctors
v. There are numerous small producers with no market power
vi. The consumer is sovereign
vii. Consumers are rational.[148]

However, in most aspects of healthcare, all of these assumptions are violated. There is a great deal of uncertainty in healthcare. Externalities (spillover effects) can occur, particularly with public health interventions that may benefit not only the 'consumer' but also the rest of the population (and also the opposite is true as we have can see with Covid-19, where the entire population is adversely affected and not only those who get the infection). There is imperfect knowledge, with patients knowing more about their health status that healthcare insurers, and doctors knowing more about the potential treatments than the patients. Doctors also have a vested interest in providing healthcare, it is how they get paid; and patients tend to rely on their opinions regarding treatment options. Neither the medical technology industry nor doctors are 'numerous' relatively speaking, and so they do have market power, and whilst the patient is priority, technically they are not sovereign as there are multiple influences on the provision of healthcare, including the organisation of healthcare itself. Finally, no one who is unwell is completely rational: people who are patients are vulnerable and rely on others to support and interpret information for them to make treatment decisions. Therefore '*market failure*' is the norm in healthcare.

Consequently, for most of healthcare the price paid (or charged) is not a true reflection of its value, which results in either too much or too little being produced, with consequent inefficiencies in production. This means that using competition as a means of allocating healthcare resources is likely to lead to overtreatment for some and undertreatment for others, with a suboptimal use of resources (not to mention the health effects on patients!). As a result, most nations regulate various aspects of the healthcare services, including that of medical technology. Baldwin, Cage and Lodge suggest that in such cases regulation is justified *'because the uncontrolled marketplace will, for some reason, fail to produce behaviour or results in accordance with the public interest*'.[149 p.15] Therefore it might be said that this regulatory activity is primarily undertaken in the public interest.[149] However, it may also be argued that private interests can influence regulation, or as Stigler puts it, they may *'acquire regulation'*, which '*is designed and operated primarily for its benefit'*,[145 p.3] which brings us to the alternative explanation for regulation - the private interest theory.

4.3.2. Private interest theory

Stigler suggests that industry may benefit from state regulation in several ways, including:

- Cash transfer to industry[i]
- Entry control, through price policies (e.g. price limits), vertical integration, or licensure
- Policies suppressing substitutes or promoting complementary goods/services
- Price controls (e.g. price-fixing)[145]

Therefore, there are good reasons why industry might want to acquire regulation. However, regulation also places burdens on industry. Regulation is generally costly to industry, and it allows industry 'outsiders' to have an influence on the industry, in the sense that the regulatory bodies, and indeed the regulatory process, admit other influences besides those from the industry.[145] Regulation also leads to a redistribution of power within the industry, often changing the level of control of the industry that one set of firms has compared to another. Stigler argues that, at least in the context of the introduction of production quotas, this redistribution usually favours smaller enterprises, giving them greater control of the industry when compared to the same situation without regulation.[145] However, regulation that produces barriers to entry in fact increases the power of the incumbents. Therefore, Stigler hypothesises that *'every industry or occupation that has enough political power to utilise the state will seek to control entry'.*[145, p.5] This can be achieved in three ways:

- Imposing entry requirements
- Introducing controls that slow the growth rate of new entrants
- Using tariffs to create a barrier to movement

However, this means that the introduction of state regulation is an intrinsically political process,[150] because it introduces a different mechanism of resource allocation. The democratic political decision-making process differs from the market process of resource allocation, because democratic decisions must be made simultaneously by a large number of people (which Stigler calls *'simultaneity of decision'*) and the decision process must involve everyone[ii] in the democracy even those who are disinterested in the decision (which Stigler calls the *'universality of political decisions'*).[145, p.10]

Due to the impracticality of everyone voting on every single decision to be made, together with the need for simultaneity of decision-making, has meant that democracies have adopted an approach whereby they elect political representatives to take people's

[i] For example, via subsidies or bonuses.
[ii] At least everyone with voting rights.

preferences into account, investing them with the discretionary power to make decisions on behalf of a large number of people at the same time. However, political representatives cannot take *'marginal changes in preferences'* into account, nor can they generally predict the preferences of their voters in advance.[145, p.10] Furthermore, the universality of decision-making means that decisions are made without all those affected by the decision necessarily being interested or knowledgeable regarding the decision options. Consequently, Stigler asserts that *'the political system does not offer good incentives like those in private markets to the acquisition of knowledge'*.[145, p.11] This point will be returned to later in the thesis.

Although the political system doesn't incentivise knowledge acquisition by citizens on all topics that require policy decisions, this may be modified through instituting several levels of government, therefore, citizens can become more involved at a local level of government and/or can acquire knowledge relevant to that level of government. Additionally, elected representatives are frequently members of a political party, who are incentivised to find out what their voters want[i], in the hope of being rewarded with their votes.[145] However, there is no guarantee that they will win the votes, making politics a balancing game of deciding who to please when. In order to remain in power and so have the decision-making capacity to influence policymaking, politicians must balance the desires and the good of the voters with the desires and the 'good' of industry or of other powerful actors who can influence whether the politician or party remains in power. Therefore, decisions that promote the public good but hurt the politically powerful industries may lead to the subsequent demise of the politician's or party's power to do good in the future. Stigler argues that this means that political representatives must therefore *'find a coalition of voter interests more durable than the anti-industry side of every industry policy proposal'*.[145, p.11] Of course, the alternative is that they use their discretionary power of decision-making to favour industry preferences.

Stigler suggests that the political system works in such a way as *'to implement all strongly felt preferences of majorities'*,[145, p.12] some of the strongly felt preferences of minorities but in general disregards less strongly held preferences by either majorities or minorities.[145] Therefore, in order for industry to *'acquire regulation'* it must provide the political representatives with what they need to stay in power, namely votes and resources (funds or services).[145] The cost of obtaining legislation (by industry) is likely to increase with the size of the industry due to the increasing costs to society of such legislation but Stigler suggests that this rise in cost (of obtaining legislation) is likely to be smaller than the increase in the size of the industry because of the *'fixed size of the*

[i] Consequently, they acquire the knowledge relevant to those issues.

political "market"', which he argues effectively precludes smaller industries from the political process.[145, p.12]

Thus, in this way Stigler provides a rationale for the private interest theory of regulation, which Posner refers to as regulatory capture.[150]

4.3.3. Other explanations

Sometimes, competition is not the best approach for the allocation of resources in either the public or the private interest. For example, in contexts where networks are required to distribute a good or service, competition might lead to a loss of efficiency due to a lack of connectivity or interoperability between networks if network providers are competing. This is particularly true for services such as the provision of utilities (i.e. electricity, gas, water, and waste services), transportation services, and communication services (e.g. internet, telephone, television, radio).[149]

There are also other reasons why regulation may be required besides addressing market failure or why regulation might actually be beneficial to both public and private interests. The theory of perfect competition assumes that the regulatory goal of markets and competition is efficiency in allocating resources, but efficiency is not always the goal, nor even the most important one amongst multiple competing goals for regulation. For example, when society values human rights over efficiency, or when it values the provision of goods or services on the basis of need rather than the ability to pay for them, or when it takes account of the needs of underserved populations or future generations, as is particularly the case with public goods, then society is choosing to regulate on the basis of social solidarity and human rights rather than to achieve the most efficient allocation of resources.[149]

Bounds approaches the question of 'why regulate' differently.[151] He proposes a typology of regulation based on four broad reasons regarding why regulation might be introduced.[151] Firstly, if differences between operating conditions make compatibility between situations or entities either impossible or difficult, then regulation may be introduced to ensure interoperability by specifying the standard.[151] For example, the traffic lights system only works because there is an accepted agreement that 'green' means go, whilst 'red' means stop. The actual colours are immaterial, 'green' does not actually *mean* 'go' and 'red' does not *mean* 'stop', what matters is that everyone understands them to mean the same thing, signalling the same interpretation and response to them. Bounds calls this type of regulation '*arbitrary regulation'*, where the 'standard' is not a matter of being right or wrong, but merely an agreement to conform to a specified standard.[151] Secondly, if a situation calls for a certain standard of behaviour so as to ensure either the safety or the success of an endeavour, then regulation may

be introduced to establish a minimum level of acceptable behaviour, for example health and safety regulations ensure that employers maintain an adequate level of safety in the work environment to ensure that the risk of accidents or occupational injury is kept to a minimum. This he calls *'good faith regulation*'. Thirdly, if there are conflicting values, norms, or goals held by different strands of society, or even competing within an individual, then regulation may be required to address these conflicts, to specify which should hold greater weight and when. This is '*goal conflict regulation'*. For example, where the right to free speech allows someone to make false claims about a product, but the advertising authority of a nation requires that false claims are not made and holds them accountable to ensure that the public is not misled. And fourthly, when an outcome is dependent on, or heavily influenced by, the *way* in which it is conducted, then regulation may be necessary to specify how to achieve the desired outcome through '*process regulation*'.[151]. This is particularly true where standardisation of a product or a process is desirable and where excessive variation (e.g. from design specifications) can lead to failure or poor results from the product or process. Thus, according to Bounds typology the four types of regulation are:

- arbitrary
- good faith
- goal conflict
- process regulation

Nevertheless, each of these might also be viewed as specific cases applicable to either the public interest theory or the private interest theory of regulation[i].

The next section discusses the possible reasons for regulating medical devices specifically.

4.4. Why regulate medical devices?

Drawing on the theories described above, the reasons for regulating medical devices, theoretically, include the possibility of addressing market failure in the public interest, regulating for private interests. Each of these will be discussed taking the peculiarities of medical devices into consideration.

4.4.1. Market failure reasons

From the public interest perspective, there are several reasons that market failure might prompt governments to regulate medical devices. Although there are multiple manufacturers of medical devices, within the individual product categories there are

[i] It is also possible that both interests align and regulation is brought in to benefit both the public interest and private interests.

fewer numbers of producers, in effect creating an oligopoly[i], and thereby potentially reducing competition and increasing those product prices. Patients generally have little or no information on the implants that they receive, demonstrating significant information asymmetry. There may also be inadequate information as well as information asymmetry between manufacturers and the users of devices because the manufacturer (though more usually the distributor) can be expected to portray their device in a positive manner in order to sell it, whilst the users of implantable medical devices, who are generally surgeons, rely on the distributor or the manufacturer to provide them with information on how the device works and how well it performs. Manufacturers and distributors are also, to a certain extent, reliant on feedback from consultants using their devices to know how well they do actually perform and what the patients' clinical outcomes are. The manufacturing process for medical devices is a highly specialised task, that if not performed well poses risks to patients' health and safety. Thus, standardisation is important to ensure consistency in quality, but this increase in quality comes at a cost, resulting in competing objectives for manufacturers. Therefore, goal conflict regulation may be needed. For all these reasons regulation of medical devices is warranted in the public's interest.

4.4.2. Private interest reasons

Industry, as Stigler asserts, will exert any power it has to reduce market entry by competitors.[145] Manufacturers and designers of innovative devices invest heavily in their innovation,[153] so they need to recoup those costs with sufficient profits to generate an income. In the medical device industry new products may be patented, but that does not prevent the emergence of sufficiently similar devices that can compete with the originator within a very short time period after the original product has been launched on the market. This may be because of the reputedly short product lifecycle for medical devices.[154] Therefore, incumbent firms (manufacturers in particular, but potentially also distributors) may seek regulation to prevent or reduce entry to the industry by potential competitors. However, as regulation is costly to implement for all economic operators, they may also oppose regulation that makes onerous demands of them.[145] Therefore, they may seek to influence regulatory policy for their benefits by limiting its extent, or by

[i] Data on this is difficult to ascertain, but a report on a market review of economic operators placing surgical mesh implants for urinary incontinence or pelvic organ prolapse on the French market conducted in France by the national regulator of health products, ANSM, identified 21 companies supplying the French market. Of these, there were 18 manufacturers of surgical mesh for treating pelvic organ prolapse (selling 59 different product ranges), 15 manufacturers of surgical mesh for female urinary incontinence (with 37 different product ranges), and just 6 manufacturing surgical mesh for male urinary incontinence (6 ranges of product). These numbers may suggest possible scope for healthy competition, but ANSM report that 85% of the sales volume in 2017 was sold by just 7 of these companies. More than 61,000 of these devices were sold in France in 2017 alone.[152]

shifting the costs of meeting the regulatory requirements on to others, such as the public, institutions, governments, or supranational organisations. Thus, there are several reasons why industry might wish to acquire or influence medical device regulatory policy.

4.4.3. Human rights and social solidarity reasons

One of the ethical principles held by most doctors is *primum non nocere* – first do no harm, whilst in healthcare there are four commonly held ethical principles guiding professional conduct, namely autonomy, beneficence, nonmaleficence, and justice.[155–157] The principle of autonomy means that clinicians should respect patients' informed choices, whilst the principle of justice requires that treatment decisions should be fair, both for the individual and for the population. The principle of beneficence reflects the goal that all doctors should have, which is to improve the health and wellbeing of their patients, whilst nonmaleficence indicates that he/she should cause no harm. However, as it states in the ethics guide for doctors, *'Providing medical treatment necessarily involves some degree of risk. However, you must ensure as far as possible that the services and treatments you provide are safe and comply with the standards of the profession.'*[158 point 18.1] And indeed, most medical and surgical treatments carry a risk if not an actual occurrence of harm, but this is usually considered acceptable if the expected benefit is greater than the harm. For example, a blood test will cause minor, but, nevertheless, real harm to a person, but this is considered acceptable to most people, even though it is just to diagnose conditions rather than actually treating them. The expectation that doctors will 'first do no harm', or at least attempt to balance beneficence with nonmaleficence, may be considered, thus, to be a right of patients receiving care. However, it may be that not all doctors uphold these values,[159] or they may not have the training and skills to appropriately balance beneficence and nonmaleficence to provide the best care to patients. Consequently, regulation is generally thought to be necessary to ensure patient safety when there are significant risks of harm arising from any treatment, particularly where this involves surgery or implantation of artificial parts, and especially when these involve novel devices or procedures. Similarly, regulation is also considered appropriate to prevent or challenge false claims being made about a product, so as to uphold the right to not be misinformed or misled by false claims. In addition, many societies consider that there exists a right to compensation for damages done due to the use of a faulty product, and frequently this is enshrined in some form of consumer protection legislation.

Whilst not really the focus of this research, the equitable distribution and fair access to medical technology is frequently regulated by governments to meet the healthcare needs of geographically distanced populations, minorities or socially disadvantaged groups,

although this is generally instituted at the policy rather than the legislative level. One such allocation mechanism is the application of HTA to explore the issues and to provide those responsible for resource allocation decisions with the information needed, and often also advice, recommendations, or stipulations depending on the jurisdiction. Since this involves the allocation of public resources this also requires some form of regulation.

Taking Bounds' typology of regulation into account,[151] arbitrary regulations may be required to standardise manufacturing outputs. The design process is complex, with many potential pitfalls, therefore, good-faith regulation may be deemed necessary to ensure that a sufficiently rigorous design process is followed. In all businesses, there is a tension between providing a high-quality product or service and keeping costs to a minimum. In general, costs can only be reduced at the expense of reducing the product's performance or by increasing its risks.[160] Therefore, process regulation may be required to ensure that medical devices are produced at an acceptable level of quality. With the competing public interest goals of increasing innovation and competitiveness yet also requiring high-quality healthcare, goal-conflict regulation may be required to mediate between these, sometimes, conflicting objectives.

Clearly there are multiple reasons why governments might regulate medical devices and health technologies. Furthermore, WHO is a strong proponent of the regulation of medical devices, asserting that it is necessary for governments to implement regulatory policies for medical devices, addressing all aspects of importance across their lifecycle, in order to assure high-quality and safe medical technologies that are appropriate to the healthcare system.[109] This includes policies regarding the quality of design and manufacture, appropriate advertising and conditions of sale, and their safe use and disposal. They also suggest that *'policies will be unsuccessful unless they are translated into national regulations that are enforced by legislation and correlating sanctions, and that form an integral part of the overall health system.'*[97]

4.5. How does regulation work?

The public interest theory of regulation would suggest that the goal of regulation is to solve a societal or economic problem, and it does this by targeting the supposed causes of that problem. Regulation seeks to effect a change in behaviour to bring about the desired change in a specific outcome or outcomes. Based on this understanding, and in order to explore and evaluate the process in more detail, Coglianese breaks up the regulatory process into seven steps, from A to G.[143]:

'The basic elements of regulation, behaviour, and outcomes (both desired and undesired) form the core of any model of how regulation is supposed to work. Figure 4.3

builds on those core elements to present a relatively simple schematic of regulation and its impacts. It maps out in a general way the relationships between distinct steps in the development and implementation of any regulation, leading to its eventual effects. Coglianese's model shows that regulation itself comprises not only a rule – but also that its effects will be influenced by how that rule is implemented and enforced. In addition, the schematic makes clear that both the rule and its implementation are products of a regulatory process, carried out by decision makers in specific regulatory institutions who must operate under their own set of rules and practices. Finally, regulation not only affects the behaviour of those targeted by a rule and its implementation, but the behavioural change induced by a regulation can lead to several different kinds of outcomes, desired and undesired, intermediate and ultimate.' [143 p.10]

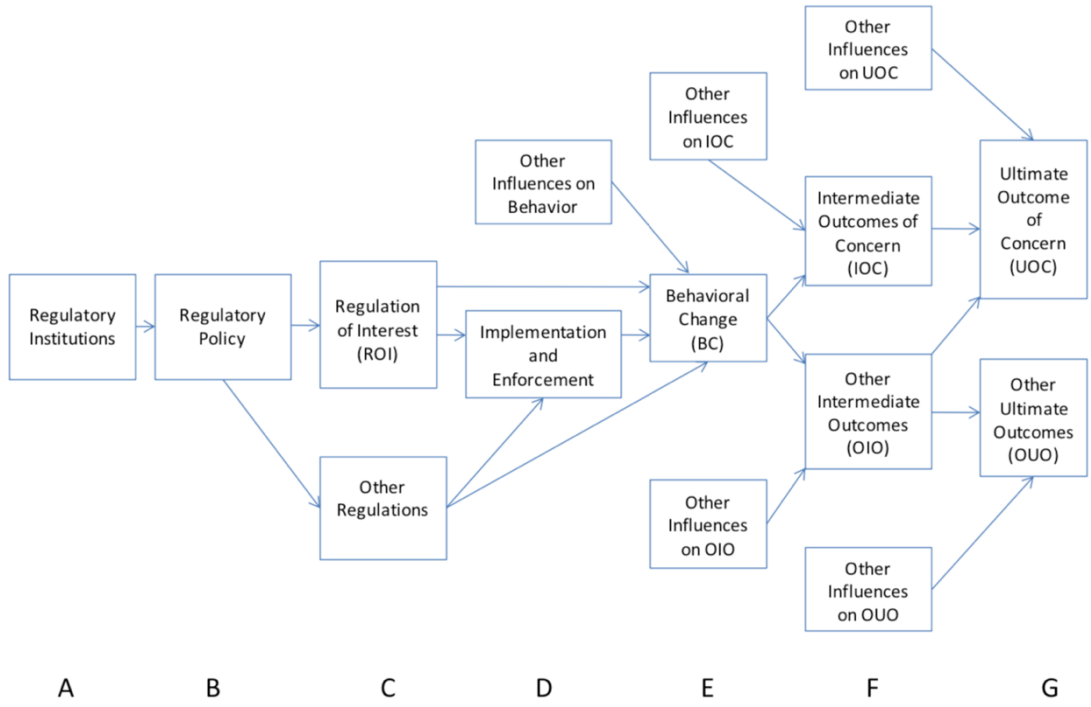


Figure 4.3: A causal map of regulation and its effects (extract from Coglianese 2012)[143]

The first step, Step A is the 'Regulatory Institution' which decides on the regulations or rules to be imposed. Step B is the way in which the regulatory institution operates, its policies, practices, rules and operating procedures which for simplicity he refers to as 'Regulatory Policy'. Step C refers to the actual rule or set of rules devised and enacted by the regulatory institution to address a regulatory goal, that is the 'Regulation'; Step D is the implementation process and the enforcement methods used to implement and enforce the regulation, included under the umbrella term of 'Implementation'. The next stage in the regulatory process is the behaviour change which the regulation seeks to effect, and other behaviours that change as a result even though they were not the

specific target of the regulation. Step F looks at the intermediate outcomes that result from the changed behaviours, some of which are necessary prerequisites or influencing factors to effect the 'Ultimate Outcome of Concern' in Step G, but some are ancillary, unwanted or unrelated 'Intermediate Outcomes' or 'Other Influences' on the 'Ultimate Outcomes of Concern' or on 'Other Ultimate Outcomes'. Step G focusses on the ultimate outcomes, both those that the regulation seeks to address and other outcomes, such as changes or effects on costs, innovation, equity, etc. Thus the regulatory process consists of a regulatory institution, governed by its policies and practices, developing and instituting a regulation, which is implemented and enforced, resulting in a change in behaviour of the regulated entity (though this behaviour is also influenced by other factors), which leads to intermediate outcomes that, along with other influences, result in the ultimate outcomes, both intended and unintended.[143] This is essentially a logic model or programme theory of how regulation works. I used this to structure the examination of the legal framework for medical devices in the next chapter.

4.6. What are the different means of regulation?

This depends on the definition of regulation used, whether it is the set of rules, state intervention, or all mechanisms of influence, each of which will now be considered.

***The Rules*:** 'Rules' can be hard or soft, that is written in law and policy statements, or unwritten societal norms and values. Focussing on written rules as explicit deliberate interventions to influence behaviour, for the most part the means of regulation takes one of four different approaches to regulation (i.e. changing behaviour) – the rule may direct the regulated entity to: adopt a specified means; achieve a particular end (e.g. a target or a limit); disclose information; or it may require the regulated entity to plan and develop its own set of rules to apply to address the regulatory problem.[144] In order to be effective, there must be consequences for non-compliance. The consequences of non-compliance/compliance with the rules can be negative, in the form of a penalty (e.g. fines, loss of privilege, loss of licence, etc.), or they can be positive, in the form of a reward (e.g. awarding a licence, approval, or exemptions of some sort). The consequences may be all-or-nothing (binary in form) or they may be incremental in nature.[144] However, to be effective the rules must be implemented and enforced. Those rules that are enshrined in law carry more force than those that are written into policy documents, but even laws may not be implemented or enforced.[161]

***State Intervention*:** Economists generally assume this definition of regulation, and Litan suggests economists consider regulation to be of two main types – economic, and social.[162] Economic regulation serves to employ rules that control entry to an industry (entry controls) or what price may be charged for certain goods (price controls); whilst

social regulation refers to rules governing the behaviour of the regulated entity in the context of 'market failure'.[162,163]

Pritchett considers there to be three main approaches to regulation, namely '*command and control*' or '*means-based*' regulation, '*performance-based*' regulation, and '*management-based*' regulation.[164]

- ***Means-based* regulation** specifies the '*methods, materials, and the processes by which the regulated entity must operate*.'[164]
- ***Performance-based regulation*** does not specify the materials to be used, nor the processes to be adhered to, but instead sets a target, limit or standard that must be achieved.[i]
- ***Management-based regulation*** neither specifies the means nor a target to achieve, but rather requires that the regulated industry or sector *'self-regulate'* by setting their own standards, with individuals (or individual firms or organisations) being evaluated against those standards either through a self-evaluation process or through an external evaluation process by an independent third party.[164]

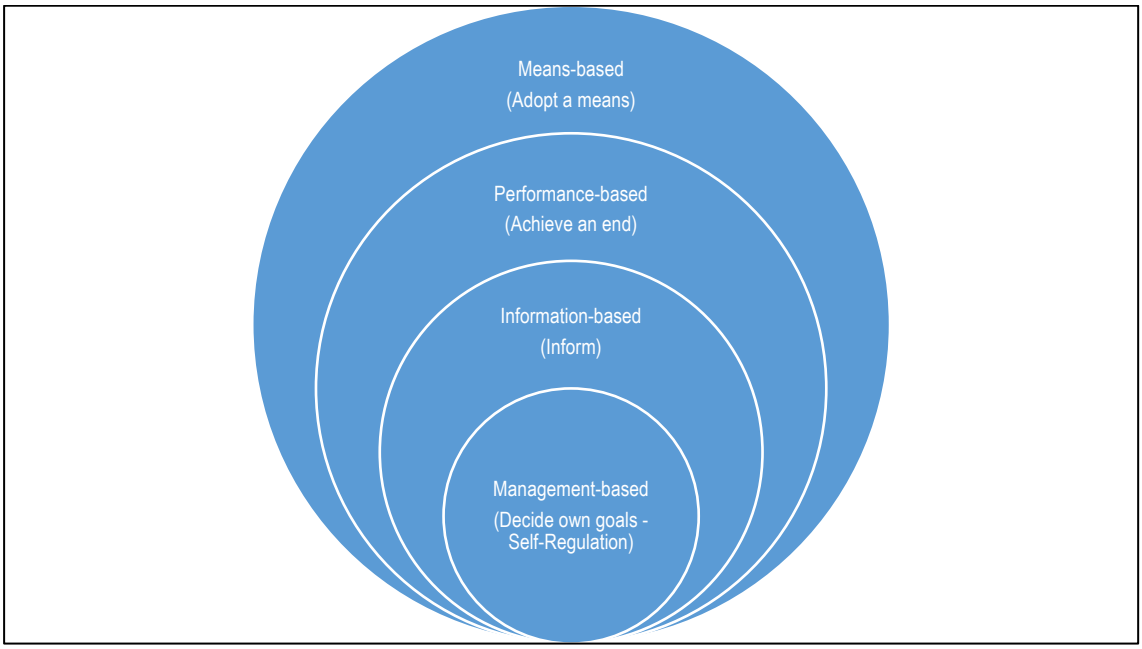


Figure 4.4. A hierarchy of regulatory tools

To these three, Coglianese adds the possibility that regulators may require that information be disclosed, which he suggests can be an end in itself or the means to achieving an end (e.g. where information stimulates a particular action).[144] Thus, a state may impose one or a combination of these types of regulation on industry or another

[i] Pritchett comments on the fact that performance-based regulation can result in privileging some societal goals over others. This is important to consider when looking at the standards that have been set or are being set.

regulated entity, the choice of which depends on the intended goal, and to a certain extent, their power to impose it. Means-based regulation is generally stronger than performance-based regulation, which is more powerful than self-regulation, whilst requiring information varies in its power to effect behaviour change depending on the context, who is informed, and what the information is. For example, they could require medical device manufacturers to adopt specified design and manufacturing processes and specific components or biomaterials to produce their devices; or require that they meet specific standards for these. Alternatively, if they have little power, they could require them to determine which are best themselves (i.e. self-regulate) and inform the regulators what system of self-governance is being applied.

***All mechanisms of influence*:** Deliberate regulation may be introduced outside of state interventions through the establishment of international agreements or treaties, which may remove or impose barriers to free movement of people or goods. Unintentional regulation might also occur indirectly due to externalities, such as the spillover effects from increased learning, pollution, healthy lifestyles, environmental protection policies (and many others) that spillover onto the neighbouring nations of the country which has 'produced' these effects through their regulation. For example, requiring that a certain standard be attained for a device entering one state's market may result in more devices being produced to meet that standard, thereby improving the quality of devices available on the market in other countries.[97,108] However, it may also mean that devices that fall below the specified standard are, in effect, dumped on the markets of countries with less stringent requirements, and this is a significant risk for LMICs with less developed regulatory systems.[165–167]

Whilst he lists various forms that regulation may take, Coglianese overcomes the difficulty of classifying or categorising regulations into different types by elucidating four core components intrinsic to all types of regulation regardless of the regulatory form they take.[144] These are the regulator, the regulatory target, the command or the rule, and the consequences.[144] The regulator is the entity that creates the rule and dispenses the consequences, although sometimes the rule-maker may not be the actual rule-enforcer. The target is the individual or the organisation to whom the rule is applied and who takes the consequences for compliance/non-compliance. The command is the rule being enforced. The consequences are the specified or actual outcomes that result from compliance or non-compliance with a particular rule. Considering regulation in terms of its core components provides an analytic framework for examining a regulation in terms of what it is regulating, how, by whom, and to what extent, since the combination of these four core components, Coglianese argues, affects the flexibility available to the regulator

and the target, and influences the behavioural incentives.[144] Therefore, I used this as an analytic tool for analysing specific legislation.

4.7. Who regulates?

Who 'the regulator' is deemed to be depends on whether we are considering the rule-maker or the rule-enforcer, since they are not always the same entity. It also depends on which definition of regulation is being used. The rule-maker might be specified in *The Rules* as the entity responsible for establishing the implementing rules for that piece of legislation. For *State Interventions* the rule-maker would be the entity or institution that drafts and enacts the policy or legislative instrument that regulates an activity. However, the rule-maker need not necessarily be a regulatory body or institution, it could be some other policy-making institution that uses other means of regulation rather than legislation (e.g. applying social incentives, teaching new skills, broadcasting key information, and so on). Considering *All mechanisms of influence,* the rule-maker could be any entity that introduces some regulatory mechanism that impacts on behaviour, deliberately or unintentionally. One example of such an entity would be the international or transnational organisations that publish accords, agreements or targets that individual countries are expected to strive for, or to meet, such as the international trade agreements negotiated through the World Trade Organization (WTO), or their capacity building initiatives such as training events or workshops; or the targets set by the United Nations (UN) for example through the Millennium Development Goals.[168–171] It could potentially even be an interest coalition that publishes a statement to put pressure on governments, such as the Implant Files published by the International Consortium of Investigative Journalists (ICIJ) exposing the lack of regulation for medical devices, because they are pressurising governments to impose stronger regulations on implantable devices.[6] Thus, who is meant by the 'rule-maker' clearly depends on the meaning attributed to regulation.

Similarly, for the 'rule-enforcer', the entity held responsible for implementing the rules (in the sense of explicating how the rule must be met), monitoring compliance, and issuing the resultant consequences for compliance and/or non-compliance also differs according to the definition of regulation, but it also varies depending on what is being regulated. For example, rules are often implemented and enforced by a regulatory authority specific to that field, such as the competent authorities in the case of medical devices who are responsible for implementing 'state interventions' (if we consider the EU to be a state) or the notified bodies designated to assess medical devices under 'the rules' for medical devices. Considering all mechanisms of influence and deliberate supranational interventions specifically, such as the publication of a model regulatory framework for medical devices intended for use globally,[172] the rule-enforcers are generally peers within

a stakeholder group, such as the World Trade Organization or the Global Harmonization Task Force, who see harmonisation as beneficial to all involved.

Regardless of who the regulator is, the power to make and enforce rules varies according to how the rule-maker and the rule-enforcer gained their authority to perform these tasks. The power to make or enforce rules may be vested in them in one of three ways – it may be attributed by their peers (least powerful), established in legislation (more powerful), or intrinsic to their position of power (most powerful). This last form of authority (fiat regulation) means that the rules once made are automatically enforced.[151] How effective a regulation is at achieving its goals largely depends on the power of the regulator as well as the strength of the actual rule to effect change. The next chapter takes this into account, examining the power of the regulator and the strength of the rules set out in the legislation governing medical devices in the EU, to assess how well it can achieve its goals.

4.8. What is regulated?

This section briefly considers what is regulated. Regardless of which definition of regulation is used, there are three potential aspects that may be regulated, namely the person or people conducting the process, the actual process itself, or the products of the process. The forms regulation may take depends on which of these three is being regulated.

Coglianese calls the entity that is being regulated the *'factual trigger'*, meaning that if something comes within the scope of the regulation then those responsible for that entity are subject to that regulation.[144] For example, in the Medical Device Regulation (MDR) any product (not subject to any of the exceptions) that meets the definition of a medical device specified in Article 2, is the factual trigger placing the responsibility for meeting the applicable requirements set out in that legislation on the device manufacturer (or other relevant specified economic operator).

Sometimes, the factual trigger may be an individual entity while the regulation may specify a wider *'frame of reference'*, meaning that the rule may apply to a group or an industry even though the factual trigger occurs at the level of the individual person or firm. Thus, the rule may apply to an industry though it is enacted at an individual level. One example of this in the medical device field is the application of a rule to a batch of medical devices, where the factual trigger (i.e. it triggers the rule) is a single device, but the frame of reference is the batch produced by a single manufacturing run, such as the statistical control of production processes by sampling batches to check for non-conforming devices. Individual non-conforming devices identified in the samples are not approved, but the batch is accepted if less than 7% of sampled devices are non-

conforming.[1 Annex IV 6.3] Coglianese gives the example of a regulation to limit air pollution, the factual trigger is the presence of a smokestack, signalling that the building or the firm that owns or uses it is subject to the regulation, but the frame of reference for the regulation may relate to limiting emissions from a single smokestack, or from the overall set of smokestacks from a single building or firm, or alternatively it may even be a limit that is applicable at an industry, regional or nation-wide level, thereby potentially allowing emissions trading between companies, industries, or even countries.[144] Thus, the frame of reference matters, because the rule may not result in the desired effect if it shifts the problem it is meant to address somewhere else.

4.9. Conclusion

Stigler argues that 'The central tasks of the theory of economic regulation are to explain who will receive the benefits and burdens of regulation, what form regulation will take, and the effects of regulation upon the allocation of resources.'[145 p.3] So a crucial question that the exploration of the EU legal framework for medical devices must address is why are medical devices regulated, and in whose interests are they being regulated?

To do this the theories described in this chapter have informed the methods used to examine the medical device regulatory framework described in the next chapter.

5. Research Methods

Research Questions

RQ1. What lifecycle approaches, models or frameworks have been used to evaluate medical devices?

a. What is meant by the 'medical device lifecycle' and 'lifecycle evaluation'?
b. How do these differences in meanings affect patient safety?

RQ2. How are medical devices regulated in the EU? How does this affect patient safety?

There is no standardised research method for synthesising conceptual or theoretical models and frameworks, nor for exploring legal frameworks from a non-legal, biomedical perspective with a similar research objective (i.e. to improve patient safety as opposed to arguing points of the law). Therefore, I developed novel methods. I systematised my approach by drawing on established methods and using the steps for conducting a systematic review (listed in Box 5.1) to guide me in developing appropriate methods for each of the studies, adapting each step as I encountered challenges related to the nature of the data being synthesised.

I adapted qualitative evidence synthesis (QES) methodologies to explore conceptual models and frameworks, described in Section 5.2, and a qualitative document analysis (QDA) design to explore the EU medical device legal framework, described in Section 5.3. Section, 5.1 explains my rationale for adopting these methods.

5.1. Rationale for my choice of methods

5.1.1. Study 1: Qualitative Evidence Synthesis

'Qualitative Evidence Synthesis' (QES) is the term used to describe a collection of study designs that review and synthesise primary qualitative studies.[173]

5.1.1.1. Rationale for using QES

Campbell et al, 2014, suggested that the use of qualitative research methods and tools are useful for reviews of theory.[174] Primary qualitative studies, generally, focus on exploring the beliefs, values, meaning and understanding held by people regarding a phenomenon or experience. QES reviews and synthesises these studies to create a more comprehensive understanding of a phenomenon, sometimes creating a further level of abstraction in the process.

Jackson argues that configurative reviews have value for policymakers when the body of evidence is too large to conduct a systematic (i.e. aggregative) review, which I found to be the case for this topic.[175] Configurative reviews iteratively sample and analyse the body of literature on a topic, enabling a more in-depth exploration, and frequently choose

studies for inclusion based on their contribution rather than study quality.[174,176] Their aim is to provide a more abstract level of synthesis or a more in-depth understanding of a phenomenon or an issue.[176]

Steps involved in conducting a systematic literature review

1. Describing the context and rationale (justifying the research)
2. Research question development (e.g. using a conceptual framework, such as PICO)
3. Concept development, identifying and defining key constructs, and the relevant study design (including analytic framework)
4. Developing screening and selection criteria (inclusion/exclusion criteria)
5. Developing a search strategy to identify relevant data/evidence
6. Selection process
7. Data extraction and/or coding strategy
8. Critical appraisal (examining methodological strength, limitations, risk of bias, and threats to validity)
9. Analysis – methods for deconstructing the data and examining the evidence
10. Synthesis – methods for drawing the evidence together and summarising the findings to answer the research question(s)
11. Reporting the findings & drawing conclusions
12. Making recommendations

Box 5.1. Steps involved in conducting a systematic literature review

Therefore, a configurative QES best suited my objective of achieving a deeper understanding of the meanings and impacts of adopting a lifecycle approach to medical device evaluation. However, as there is no standard QES methodology for synthesising theoretical or conceptual models and frameworks, I developed a novel approach by combining and adapting various elements from several qualitative/QES methodologies.[177]

5.1.1.2. Advantages of QES

Carroll suggests a number of advantages to QES related to clinical practice guidelines that are also relevant to QES in general.[178] First of all, he explains that the aim of QES is '*to make the most of relevant studies for the purposes of policy and practice*', and that '*the synthesis of several relevant qualitative studies can offer multiple perspectives as well as providing evidence of contradictory viewpoints that might otherwise be missed when considering a single study alone*'.[178] Furthermore, by gathering evidence from multiple studies and multiple viewpoints it is possible '*to "go beyond" the findings of such primary research studies'* and to create new understanding in addition to that which the collection of individual studies provides.[178]

5.1.1.3. Limitations of QES

The limitations of QES are similar to those in primary qualitative research, including the potential to get lost in the vastness of the data. In order to counteract this, a simple framework was used to guide the initial analysis using theory and innovative methods to compare similarities and differences to extend the final synthesis.

QES is on the expertise of the researcher, therefore, to increase my expertise in this area I attended a three-day intensive course called Evidence Synthesis of Qualitative Research in Europe (ESQUIRE), with the School of Health and Related Research (ScHARR) at the University of Sheffield in 2018, which provided me with some skill, and many resources and tools to support my research.

5.1.2. Study 2: Qualitative Document Analysis

Qualitative document analysis (QDA) is a form of qualitative research which involves the interpretation of documents by the researcher to find and present their meanings related to the topic of interest. Bowen defines document analysis as *'a systematic procedure for reviewing or evaluating documents—both printed and electronic (computer-based and Internet-transmitted) material'.*[179] He suggests that, similar to other types of qualitative data, the data in documents require interpretation *'to elicit meaning, gain understanding, and develop empirical knowledge'*.[179] QDA utilises methods and analytic procedures similar to those employed in the qualitative analysis of data from other sources (e.g. from interviews and observations), involving coding of content into codes, categories and themes. It combines aspects of thematic analysis and content analysis, whilst drawing on some of the procedures used in grounded theory or case study research.[179,180]

5.1.2.1. Rationale for using QDA

Documents are a useful source of data *'recorded without a researcher's intervention'* that can, according to Atkinson and Coffey, provide *'social facts, which are produced, shared, and used in socially organised ways'.* [179 p.30, citing Atkinson & Coffey, 1997, p.47] Documents can provide information on the background and context of a phenomenon. They can serve as the primary source of data for analysis, or as supplemental data, or additional evidence to challenge or verify facts, or to support, challenge, and extend findings from other data sources. Documents are a useful means of tracking change in a policy, the policy direction taken, or the rhetoric around that policy. Documents can also be a useful source of insight, generating additional questions that need to be asked, or explored at interviews or through observation.[179,181]

5.1.2.2. What is a 'document'?

Documents may be a form of documentation, which is the recording of an event or a phenomenon that '*signifies any process of proof based upon any kind of source whether written, oral, pictorial or archeological (Gottschalk, 1969)'*.[181 p. 19] The word 'document' can have different meanings that include all artefactual sources of information or only those that are written official communications/reports. For this research, 'document' was taken to mean any physical evidence that provides evidence or a record of the regulatory process for medical devices in the EU.[i] Documents provide information, and although documents cannot always be taken at face value, they are nevertheless one source of information that can be evaluated and compared with other sources to build up a body of evidence. The information presented on official websites, such as national governmental websites and the websites belonging to professional or statutory organisations, present the relevant official, professional or regulatory information as endorsed by that institution or organisation.

5.1.2.3. Advantages of QDA

There are several advantages to documents that make them a useful source of data for analysis. In fact, Caulley suggests that in some circumstances documents are a 'superior' source of data when compared with interviews[181] For example, interviews are dependent on the interviewer's knowledge of the subject matter and on their memory. This is not the case with documents since questions can be asked of documents at any time, and returned to and questioned repeatedly. If a document does not contain the answers then it is relatively easy to search for other documents that can provide the information. In this way documents are also very convenient, not being tied to appointment times, nor relying on the goodwill of interviewees, and once obtained they are usually not limited to a short time for questioning.

They also tend to be available at a low cost or free of charge, making them a cost-effective means of data collection in comparison to collecting original data. Furthermore, documents may be the only reliable, or the most efficient source, of data where interviews and observations are not possible or interviewees don't know the relevant details.[179,181] Caulley also argues that documents are nonreactive, which Bowen calls stability, because documents don't respond to being questioned, so their contents are not influenced by the researcher's questions.[179,181] Documents can cover a greater breadth of time, situations and settings than other sources of data, particularly regarding historical events.[179,181] Furthermore, documents have a major

[i] There are numerous types of document, and they can come in many forms, for example as books, articles, newspapers, advertisements, circulars, laws, White Papers, statistics, memos, diaries, records, reports, pictures, cartoons, and many more.

advantage over interviews when they are publicly available as they are not confidential, thus allowing the researcher to provide a more detailed and substantiated account.[179,181]

5.1.2.1. Limitations of QDA

Bowen suggests that QDA has a number of limitations related to the level of detail, retrievability, and selectivity regarding what is made available.[179] Some documents may lack details, because they weren't generated to answer the research question but for another purpose entirely.[179] Retrievability may be an issue because the document no longer exists, or is behind a paywall or some other barrier to access.[179] Access may also be deliberately blocked.[179] Documents contained within a collection may be subject to what Bowen refers to as 'biased selectivity' quoting Yin 1994.[179] This means that while many documents may have been generated by the organisation over time, nonetheless, only a selection are kept.[179] Those 'selected' to remain available may reflect organisational policy or administrative record keeping practices, so that the reason for biased selectivity may be a reflection of key players' agenda or simply a clerical practice.[179] Bowen argues that these are not fatal flaws and that the advantages outweigh the disadvantages.[179]

Caulley describes other disadvantages, which are worth taking note of, because they are relevant when considering which documents to include, and highlight the importance of seeking corroborating evidence.[181] Documents are written by people, who interpret the facts which they enter into a document, and can only include *'what the author of the document thought-what he thought had happened, what he thought ought to happen or would happen, or perhaps only what he wanted others to think he thought'*.[181 p. 21] He suggests that the writer of a document, particularly of reports, may want to make the subject appear good, for example an aid programme, and therefore be misleading. The corollary is also true. Documents may be unrepresentative, out of date, incomplete, or inaccurate with document writers making clerical mistakes, introducing biased reporting, or they may succumb to '*outright deception'*.[181 p. 21]

So, despite the limitations, I agree with Bowen that the advantages outweigh the disadvantages, and being aware of the limitations enables the development of research strategies to minimise their impact.

5.2. Exploring lifecycle models used to evaluate medical devices

A lifecycle approach to the evaluation of medical devices is warranted to identify distal causes of harm as well as the proximal causes at the 'sharp end' of healthcare provision.[91] Understanding what happens across the life of a medical device helps to

identify what can go wrong and how this might impact patient safety. Mytton et al (2010) have also shown that different questions of safety arise, and different types of risk become apparent, at different stages in the medical device lifecycle.[96] Furthermore, the factors requiring evaluation, and the evaluation methods that need to be used, also vary according to the lifecycle stage.[182,183]

This literature review was conducted to identify a suitable framework for structuring an exploration of the processes that a medical device must undergo. It was found that the concepts of 'medical device lifecycle' and 'lifecycle evaluation' are not clearly defined and appear to mean a variety of things. Consequently, it became clear that an exploration of the different meanings attributed to these concepts, as expressed in the lifecycle evaluation models, would be useful to understand what different stakeholders are evaluating and why, and whether these differences have any implications for medical device-related patient safety[i].

5.2.1. Research questions

The research questions that this study sought to address were:

RQ1. What lifecycle approaches, models or frameworks have been used to evaluate medical devices?

a. What is meant by the 'medical device lifecycle' and 'lifecycle evaluation'?
b. How do these differences in meanings affect patient safety?

5.2.2. Methods

This study drew on multiple qualitative research methods to conduct a configurative qualitative (evidence) synthesis of the literature.[176] The study's methodology is summarized in Figure 5.2.

The unit of analysis for this literature review is the model rather than the articles. Although frameworks, models, and theories have distinct meanings,[184] like Michie, Stralen, and West, I use the term 'model' to mean "*'a hypothetical description of a complex entity or process.'*",[185] to denote any approach, framework, model or theory utilised to evaluate medical devices across their lifespan (illustrated in Figure 5.2). Therefore, for the sake of brevity, the terms 'model' or 'conceptual model' will be used to encompass the entire range of theoretical or conceptual approaches, models, and frameworks throughout the thesis.

[i] This was based on the premise that if meaning is not explicit then assumptions are made, the most obvious being the assumption that people are talking about the same thing, when, in fact, they may not be, and that this may have unanticipated and untoward effects on patient outcomes.

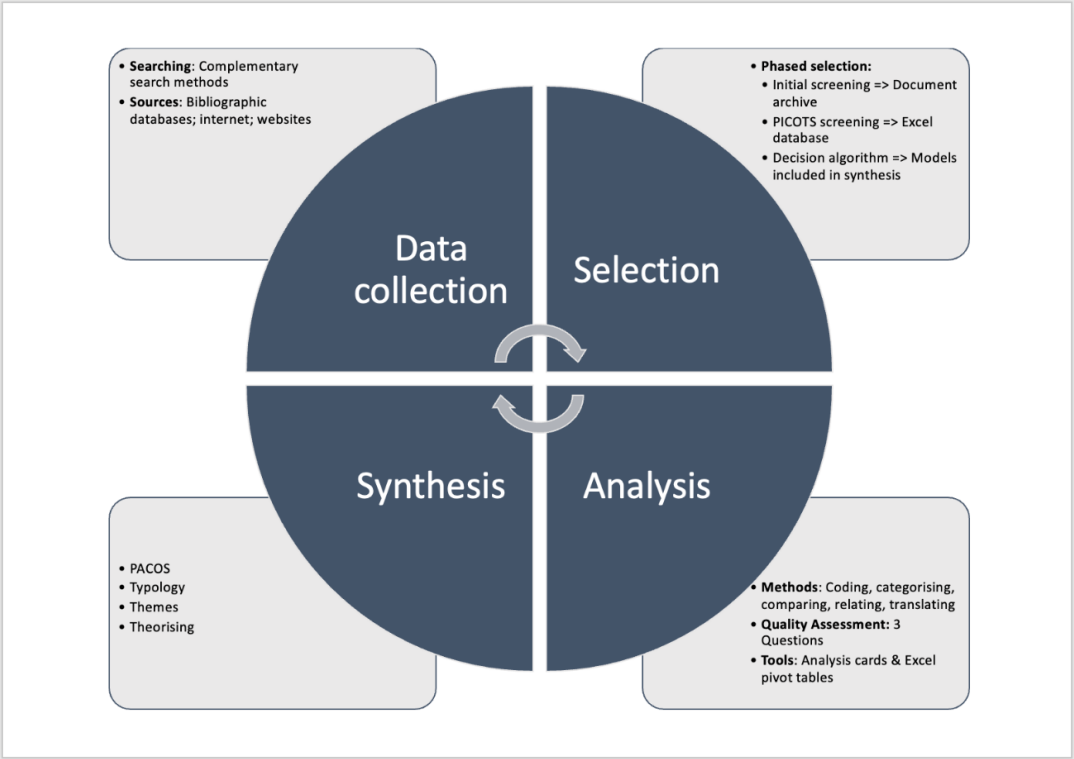


Figure 5.1. Overview of the methods used for conducting the Lifecycle Review

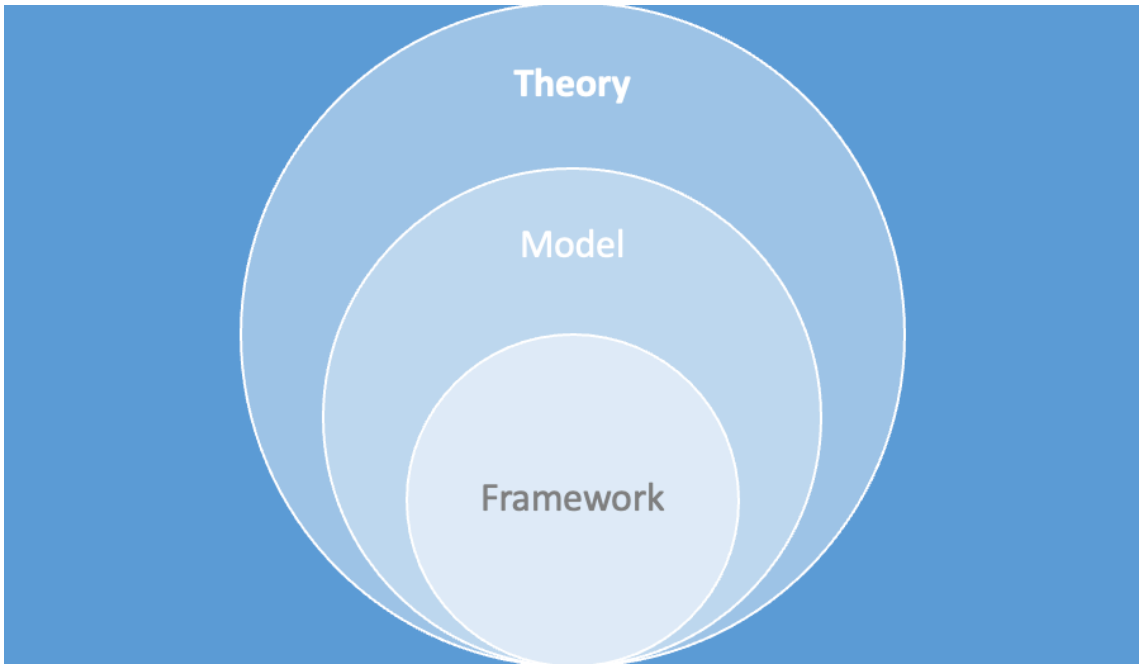


Figure 5.2. Multi-level conceptualisation of an evaluation 'model'

The included models were drawn from diverse disciplines and, consequently, demonstrated extensive heterogeneity, requiring novel methods for analysis and synthesis. These are described here using an adaptation of the ENTREQ reporting

guidelines, with more detail provided in the Tables, Figures, Appendices, and in the supplemental materials of the published article[i] based on this study.[186]

5.2.2.1. Synthesis methodology

Utilising an inductive qualitative approach, models were synthesised using analytic processes drawn from grounded theory, qualitative content analysis, thematic analysis, and meta-ethnography to create a comparative analysis of key characteristics of the models, a typology of models based on their focus of interest, and a thematic analysis drawn from the patterns observed across the models.

5.2.2.2. Approach to searching

Due to the unexpectedly large number of lifecycle evaluation approaches found in the literature, and drawing on methods previously described, a pragmatic approach to searching was adopted.[187–189] Indeed, complementary and snowball techniques have previously been found to be more effective and efficient at identifying relevant material when the topic is complex and multidisciplinary.[188,189] Seminal texts and models were identified through scoping searches conducted in biomedical and multidisciplinary bibliographic databases, the Internet and specific websites using keywords and phrases covering the concepts 'medical device', 'lifecycle', and 'model'. Snowball searching (i.e. manual searching of references, references of references, citations, and links to similar articles) of seminal texts was employed to identify additional models.

Electronic Search strategy: See article supplemental material ***Link.***

5.2.2.3. Data sources

Systematic scoping searches were undertaken in PubMed, EMBASE, and the Cochrane Library; and pragmatic searches of the internet (in Firefox and Safari browsers using Google search engine), Google Scholar, and JSTOR. Webpages were downloaded into a bibliographic software and copied into a Word document for each website. Where possible books were also obtained[ii].

5.2.2.4. Inclusion criteria

The inclusion/exclusion criteria are listed in Table 5.1. Any lifecycle model that may be applied to a medical device (such as a product, industry, innovation, therapy, technology, intervention, software or hardware, or as a specific type of device), as shown in Figures 5.4-5.5, covering several aspects/stages of a device's lifetime was eligible for inclusion. Models devised solely for evaluating medicines were excluded, because their lifecycle

[i] DOI: 10.1017/S026646232300274X, https://pubmed.ncbi.nlm.nih.gov/38179661/.

[ii] One book by Booz, Allen, and Hamilton was not found to be available. For the model described in that book I used a chapter from another book that summarised their model.

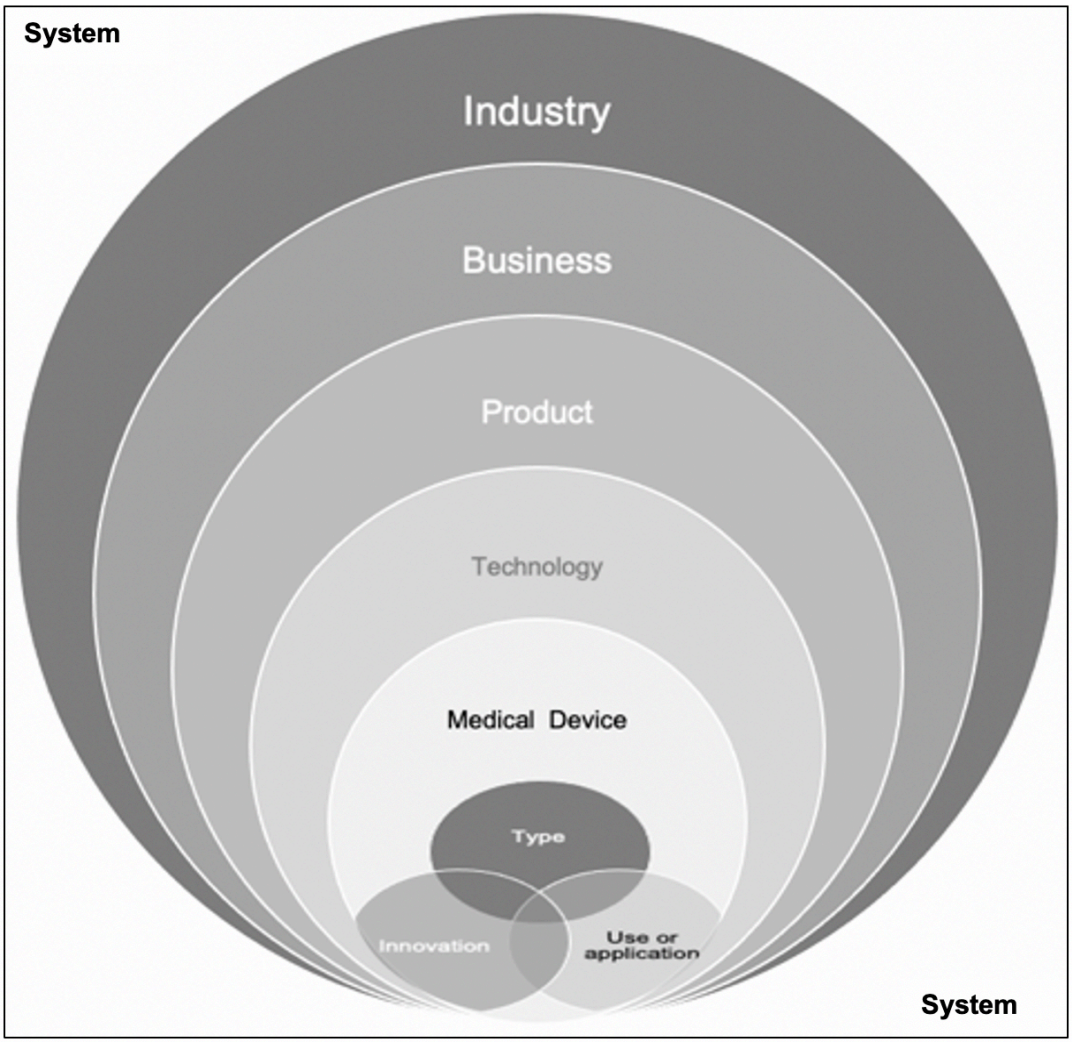


Figure 5.3. The multiple levels of conceptualising medical devices

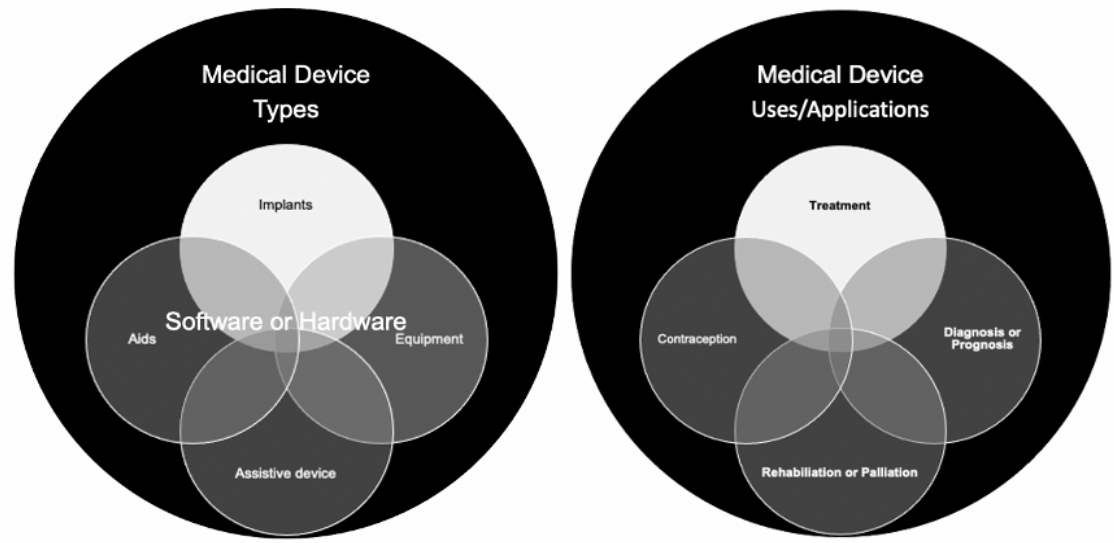


Figure 5.4. The multiple types, uses, and applications for a medical device

Table 5.1. Inclusion and Exclusion criteria

PICOTS	*Inclusion Criteria*	*Exclusion Criteria*
Population/ **P**henomenon	Medical devices Conceptualised as a specific type of device, or as a product, industry, innovation, therapy, technology, intervention, software or hardware	Medicines (excluded because the lifecycle stages are quite different, with different evaluation problems and requirements) Focus on environmental impacts
Intervention/ **I**nterest	Lifecycle, lifetime, lifespan, multi-stage, or multiple processes, activities or phases within a stage (i.e. it must cover more than one process, activity, or time point)	Single process or activity, or examines only a single point in time
Comparator/ **C**ontext	Not specified However, searches for models were conducted across those disciplines involved in medical device lifecycle activities, including design, biomedical engineering, manufacturing, marketing, regulation, HTA, procurement, health sciences, and quality management.	Not specified
Outcome/ **O**utput	Model, framework, theory, or approach to the evaluation of a medical device across its lifespan	Eco-innovation models focussed on assessing innovations to improve environmental impacts
Timeframe	Not limited	
Study Design	All 'designs' were considered eligible, including: reports, research articles, theoretical or conceptual papers, descriptive studies, guidelines, commentaries, books, summaries of books, chapters in books or webpages.	Where there were books and articles on the same topic/results the book was omitted (due to the size), and where there were chapters of books that were relevant, the remainder of the book was excluded. Summaries of books were preferred to whole texts, particularly where the book was unavailable.

stages differ considerably from medical devices, posing different problems and being subject to different requirements.

5.2.2.5. Study screening methods

Articles were systematically screened in phases against the inclusion/exclusion criteria.

- Initial screening of identified titles, abstracts, and certain full texts, was conducted concurrently with searching to exclude irrelevant texts and to identify texts with a potential lifecycle model or approach. These were downloaded and saved in a Dropbox folder, the ***Document Archive,*** for further screening.
- Archived documents were screened against the PICOTS inclusion and exclusion criteria. Data from selected texts were extracted into tables in Word and into an ***Excel Database***, and analysed concurrently.

5.2.2.6. Model selection

A **selection decision algorithm** was devised (inset in Figure 5.4) to identify the most relevant, and from that to select one representative text per model, with the remainder serving as reference materials. Searching, screening, selection, and data extraction progressed iteratively with data analysis. Selection ceased when data saturation had been reached (i.e. no significantly different models or new themes were emerging).

5.2.2.1. Appraisal items

No QA criteria have been universally accepted for appraising conceptual models. I adopted the QA criteria used by D'Amour et al,[190] assessing whether a model was underpinned by theory, empirical data, and/or an explicit literature review strategy.

5.2.2.2. Appraisal process

Models were appraised rather than articles, therefore, each criterion could be met in different sources, which meant I drew on additional texts for the appraisal process. Each model was assigned a score of one for each criterion if it was met, and totalled to provide a summary score.

5.2.2.3. Appraisal results

The QA summary scores are detailed in Figure 6.3. No model was excluded on the basis of its score.

5.2.2.4. Model and study characteristics

The characteristics of the included models and their key reference texts are summarised in Appendix 14.3-14.4.

5.2.2.5. Appraisal Rationale

Quality appraisal (QA), though its use in qualitative research is contested,[191] serves to deepen researchers' understanding of the data being examined, making the QA process valuable for increasing insight.[192]

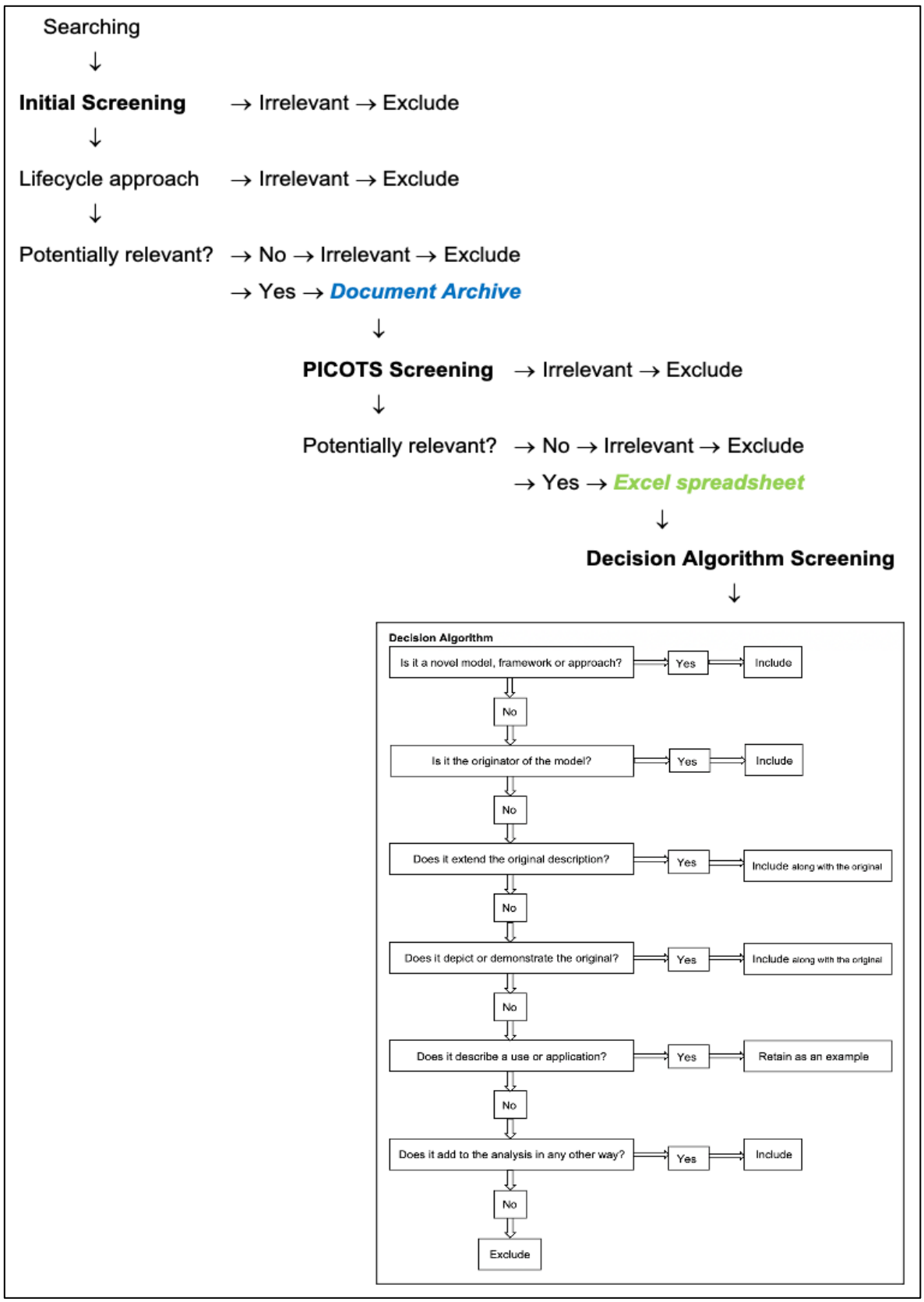


Figure 5.5. Screening & Selection Process Map

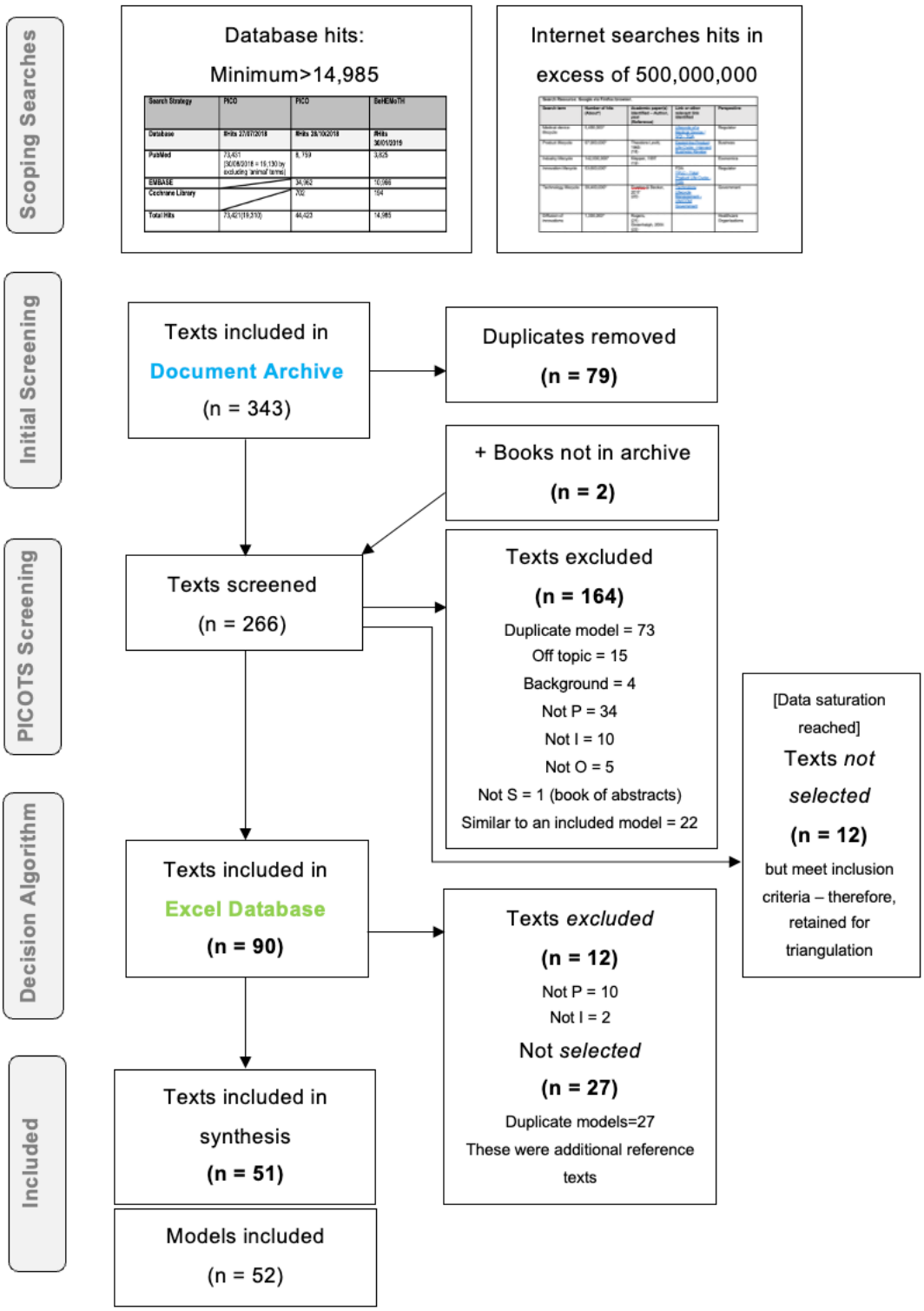


Figure 5.6. Model screening & selection flowchart

5.2.2.6. Data extraction

Data extraction tables were developed in Word and Excel as an initial coding list (Table 5.2). Data extracted included study characteristics of reference texts, model characteristics, and quality criteria. Additionally, the level of application, timepoints for analysis, process definitions, and diagrammatic/graphical/mathematical/tabular representations of the models were extracted (Figure 5.7). Data were extracted primarily from the reference text, but supplemented from others.

Software: Word and Excel 2016 for Mac (Version 16.70)

Table 5.2. Initial coding list

Document characteristics	Title First author Geographical location Year Publication Funding and conflict of interest statements
Abstract (if available)	
Explicit purpose	Purpose/Aim/Goal Objective Research question
Data related to the model	Model name given to it by the authors Model descriptions Model purpose Use Intended audience Perspective Characteristics Context Lifecycle stages

5.2.2.1. Coding

The unit of analysis is the model, consequently, coding focussed on the data extracted from the documents rather than coding each document. Familiarising myself with the models involved background reading, to understand the language used by that discipline (and to better understand the model in context), and summarising each model. The characteristics of the models were explored to develop '*dimensions of difference*',[193] Each model was categorised into one of four broad perspectives as shown in Table 5.3. Where possible, qualitative content analysis was used to reduce data[i] into broad categories (e.g. model purpose),[194] however, other approaches had to be used for other data. Visual tools were created (Analysis cards) to enable a visual comparison of the models and Excel was used to record and analyse the data, and to record much of the analytic process. Both of these will be explained further in the next two subsections.

[i] I used the approach, described by Erlingsson and Brysiewicz, where the data element was condensed into a condensed meaning, grouped into sub-categories, and grouped into more broad categories as they developed. [194]

As analysis progressed extracted data was coded into increasingly broad and more abstract categories, enabling comparison within and across categories.

Analysis Cards

A6 cards were created from the diagrams extracted from the texts. These cards were then used as an analysis tool, with various thematic categories, '*dimensions of difference'*,[193] being added to each card (Figures 5.9-5.10). The cards were used to visually compare across categories and model parameters, and to abstract and translate models. They were repeatedly sorted and rearranged according to the different categories in a similar way to the traditional ordering and reordering of codes, categories, and themes using paper format. The different representations were compared, reflected upon, and observations were noted for further analysis.

Using Excel functions

Excel was used as a database for entering data extracted directly from the documents and for analysis.

Initially rows represented unique documents. Later when a single document was chosen to represent each model, the rows were then taken to represent the model. Columns represented the data elements. Data elements were condensed into categories enabling models to be compared across different categories, including broad perspectives, using the Sort, Filter, and Pivot Table functions.

Table 5.3. Categorising the different perspectives into broad categories

Trade & Industry (19)	**Policymaking (16)**
Academia & Marketing Business Business & Academia Business & Marketing Business Management Business Strategy Economics Industry Manufacturing Industry Marketing Medical device design engineers Procurement Software Engineering	Academia, Research, Economics, Sociology & Agriculture Academic Access, Value & Sustainability EU DG GROW Health systems policymaking Healthcare & Health economics Healthcare & research HTA HTA & Economists Public Health Sociology and agricultural policymaking Space & Aeronautics Systems Engineering
Healthcare (9)	**Regulation (8)**
Biomedical Engineering & Healthcare Management Clinical Engineering & Safety Healthcare Access Surgical	Healthcare/ Regulatory Regulatory

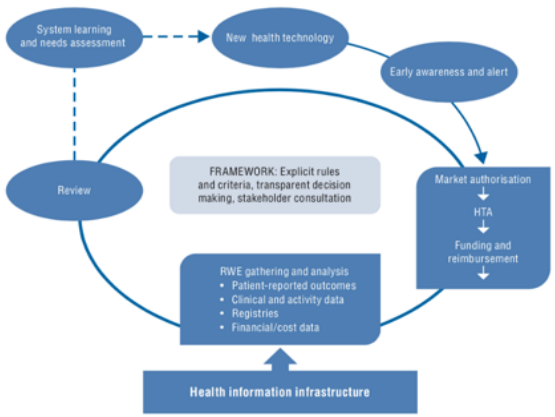
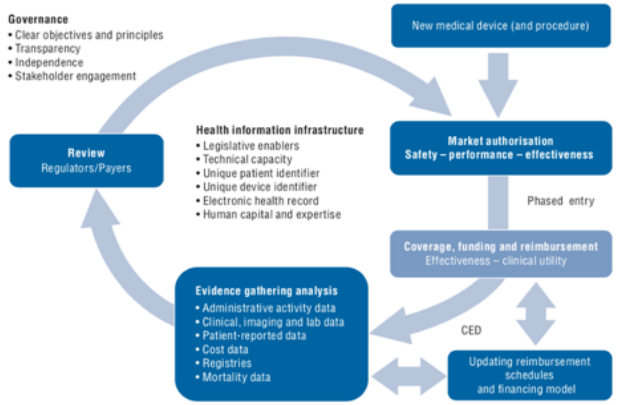
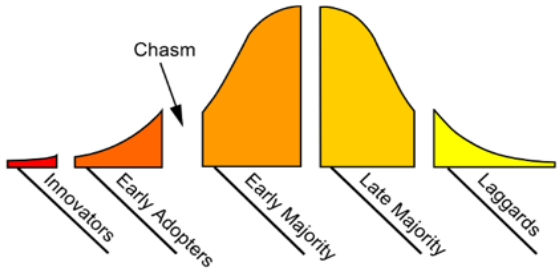
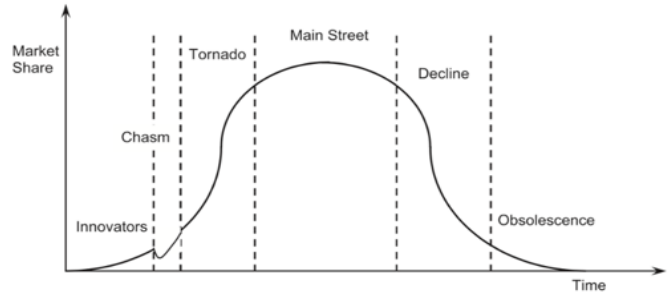
New Health Technologies – Lifecycle for integration into healthcare systems	Valérie Paris et al OECD 2017 (22) New Health Technologies: Managing Access, Value and Sustainability. 'Lifecycle framework for successful integration of health technologies in health care systems' Figure 1.2	Figure 1.2. **Lifecycle framework for successful integration of health technologies in health care systems**  Figure 4.3. **A regulatory and funding framework for medical devices and their use** 
Technology Adoption Lifecycle	Example from Meade & Rabelo (2004) (23) The technology adoption life cycle attractor: Understanding the dynamics of high-tech markets.	 Fig. 1. Technology adoption life cycle.  Fig. 2. Life cycle phases.

Figure 5.7. Extract from 'Table of Models'

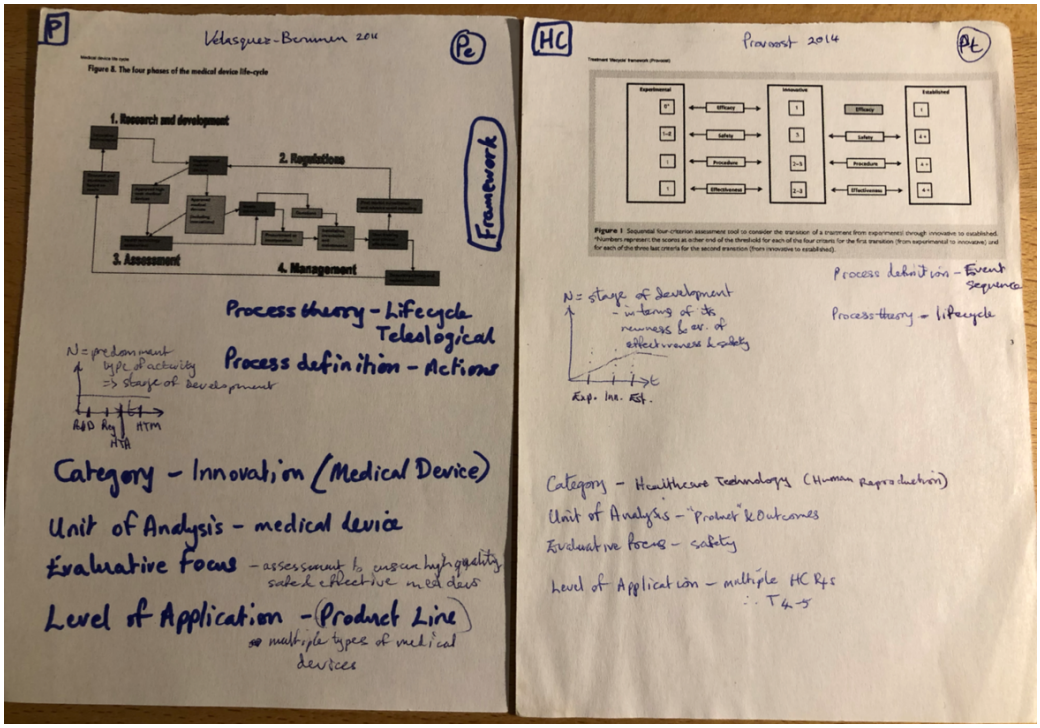


Figure 5.8. Examples of analysis cards

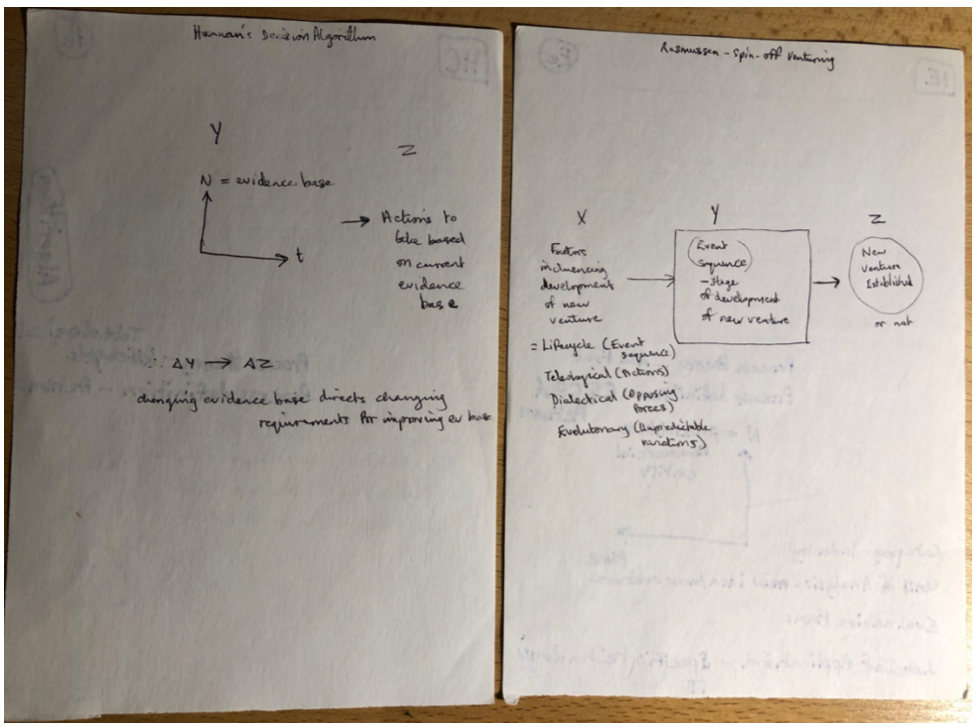


Figure 5.9: Examples of the back of the analysis cards relating the changing factors

5.2.2.2. Abstracting and translating models

Models can be represented diagrammatically, graphically, mathematically or textually. Drawing on the idea from meta-ethnographic methods, where concepts from different

studies are translated into one another, each model was transformed or translated into each of these formats[i], enabling comparison of like with like.[195,196]

5.2.2.3. Derivation of themes

Using the methods described, in a constant comparative approach, patterns in the data became apparent. Patterns identified in the models were explored conceptually through logic models and diagrams by attempting to connect issues and develop themes into a coherent framework, cross-checking those that appeared most important against the models and texts. Additional columns in excel were created to gather evidence supporting, refuting, or extending the developing themes. Reflective writing on these patterns, particularly reflecting on the assumptions underlying the developing themes, making connections between the patterns and assumptions, and comparing them with the literature elicited themes relevant to patient safety.

5.2.2.4. Trustworthiness

Definitions were developed for the data elements and interpretive elements underwent a double-entry approach (with the same question being asked differently, entered twice, and cross-checked to provide a third column of validated data) to ensure researcher consistency. Quotations are used extensively as a form of 'thick description' to justify assertions, illustrate underlying assumptions, and support arguments being made. The ***Document Archive*** is shareable, and data entered in the ***Excel Database*** provides an

[i] Using the diagrammatic representation for each model as a guide, a simple notional graph was drawn to represent the feature or factor (Y) being used to characterise the lifecycle's passage from one stage to another (e.g. number of adopters, age, or stage of development) over time. A simple mathematical notation was then used to describe the relationships between the factor characterising the lifecycle with other factors included in the model, such as features that influence (X) the lifecycle, or aspects that are impacted (Z) by changes in the lifecycle. Having identified these relationships, a brief narrative (textual) description was prepared. Thus, the diagrams were used to create graphs, which were used to derive mathematical relationships, which were then described textually. This process is illustrated in the Analysis card examples shown in Figures 5.16-5.17. The data obtained from this exercise was then entered into the excel spreadsheet so as to provide an audit trail and to illustrate comparisons made. This transforming process enabled a more abstract means of comparing models that, in particular, surfaced commonalities that were not immediately apparent between the models.
For example, the Bass model, which is a mathematical model, was drawn (on paper) by graphing N against T, where N is the number of sales and T is time. The individual sales at a given point in time produces a bell-shaped curve just like the curve illustrating the rate of adoption of an innovation over time in the Diffusion of Innovations (DOI) number of new adopters curve, whilst the cumulative function produces an S-shaped curve. Textually this may be described as the number of sales increasing over time to reach a peak when approximately half of the target market has already bought the product, before dropping again as the target market becomes saturated. Translating this again into my simple mathematical notation, the model is described as $N = dY$, which means that the model is examining changes in the factor characterising the lifecycle, which in this case is sales.
There were three types of factors included in the models – those that were used to characterise the lifecycle, factors that influenced the lifecycle, and factors that were affected by the lifecycle. I called these characterising, influencing, and impacted factors, and, in my simple mathematical notation, I referred to them as X, Y, and Z, respectively. Changes in these were represented by dX, dY, and dZ, or as ΔX, ΔY, and ΔZ. Time is inherent in all the models.

audit trail as it contains interpretive data as well as the data extracted from the texts/models.

5.2.2.1. Synthesis methodology

Utilising an inductive qualitative approach, models were synthesised by using a constant comparative method to draw out the similarities and differences, first by categorising models according to their perspective, purpose, intended audience, characterisation, focus of interest, outputs, stages, and scope (PACiOS), then transforming models from one format to another. In this way, it was possible to develop a model typology based on the focus of interest to reflect the differences in meaning for 'medical device lifecycle' and 'lifecycle evaluation', and to identify patterns in the data that highlighted key underlying assumptions that potentially impact patient safety.

5.2.2.2. Synthesis output

Several syntheses were created, including a comparative analysis of the models, the development of a model typology (archetypes), and a thematic analysis.

5.2.2.3. Reporting

The methods are reported using an adaptation of the ENTREQ reporting guidelines.[186] The findings are presented in five sections, with a brief overview first to answer RQ1. The findings from the comparative analysis are then presented in a tabular and narrative format to describe the meanings attributed to 'lifecycle' and 'lifecycle evaluation' as embodied within the models, followed by the section describing the model archetypes, to answer RQ1.a. The fourth section describes the findings from the thematic analysis, with the assumptions underlying these themes and their implications for patient safety being discussed in the discussion section, addressing RQ1.b. Finally, the conclusions sets out the key issues and potential solutions.

5.3. Exploring the EU medical device legal framework

5.3.1. Research Question

The questions that this research sought to address are:

RQ2. How are medical devices regulated in the EU? How does this affect patient safety?

5.3.2. Methods

These questions were addressed by an in-depth review of legislative and policy documents utilising QDA, describing how the regulatory process for medical devices was originally instituted, implemented, and enforced, and how it subsequently evolved. This section describes how the study's methods were developed.

5.3.2.1. *Summary of the steps involved in a QDA*

Due to limited standardisation in methods for conducting QDAs, a small number of seminal studies were examined and compared to establish an explicit research approach, defining the key components and methods for conducting a QDA. Drawing particularly on the works of Caulley 1983, Bowen 2009, Wesley 2010, and to a lesser extent Owens 2015, Cardno 2018, and Hard, Lee and Dockett 2018, the stages and steps involved in conducting a QDA were identified and summarised. [179,181,197–200].

A QDA generally starts with identifying a conceptual framework to guide the research and to provide the *'scaffolding of the study'.*[199,200] Bowen describes the next four stages as *finding* (data collection), *selecting* (screening and selection), *appraising ('making sense of'),* and *synthesising* the documents.[179] The steps involved in these four stages are not entirely distinct as there is overlap and iteration during the research process. Nevertheless, they provide a structure for conducting a QDA.

However, some of the recommended steps were not suitable for legislation. So, I developed steps appropriate for QDAs of legal frameworks, as summarised in Box 5.2.

QDA for Legal Framework Analysis

1. *Identify a conceptual framework to guide the research*
2. *Finding*
   - Creating initial lists of searching resources and key documents
   - Creating a database
   - Categorising documents
3. *Selecting*
   - Identifying the most relevant documents for the research question
   - Checking source authenticity and legal status
   - Regulatory rules of precedence
4. *Appraising*
   - Data immersion and familiarisation
   - Tracking documents and their history
   - Coding & Categorisation
   - Ensuring trustworthiness
5. *Synthesising*
   - Qualitative Description
   - Timelines & History
   - Interpretive Description
   - Deriving themes
   - Exploring possible explanations
   - Reporting

Box 5.2. A summary of the stages and steps involved in conducting a QDA for legal framework analysis

5.3.2.2. *Identifying a suitable conceptual framework*

I identified two suitable conceptual frameworks to structure the research. The multiple definitions of regulation described by Baldwin, Cave, and Lodge (in Figure 4.1) identified

three levels of (deliberate) intervention or influence: Supra/International Interventions; State Interventions; and The Rules,[142] as illustrated previously in Figure 4.2.

Coglianese's description of the regulatory process,[143] which is essentially a programme theory setting out how regulation works in a seven-stage stepwise fashion, was chosen to structure an exploration of 'State Interventions' regulating medical devices (Figure 4.3). Since the legal framework for medical devices is determined by the EU (or its predecessor), the 'State' is taken to mean the EU in this study. The steps in the regulatory process as described by Coglianese,[143] and how these were interpreted to analyse the regulation of medical devices, are outlined in Figure 5.11.

Step		Interpretation	
Step A	Regulatory Institution	≡	Rule-making institutions in the EU
Step B	Regulatory Policy	≡	Rule-making process in the EU
Step C	Regulation	≡	Rules, i.e. Legal framework for medical devices
Step D	Implementation	≡	Rule-enforcing bodies & their processes
Step E	Behaviour change	≡	The steps that a manufacturer must take to market their medical device
Step F	Intermediate outcomes	≡	CE marking → market access → user & patient access
Step G	Ultimate outcomes	≡	The goals of the regulation = to promote trade & maintain or improve safety and performance

Figure 5.10: Interpreting how the programme theory applies to medical device regulation [143]

To guide a deeper analysis of 'The Rules' contained in the MDD, Coglianese's core components of regulation (i.e. regulator, rule, target, and consequences) were chosen to assess the strength or power of each rule to achieve the regulatory goals and to ascertain to what extent they are intended for the public good or private interests.[144]

5.3.2.3. Finding (Data collection)

The process of searching for relevant documents differs to the approach used for literature reviews since most documents are not peer-reviewed articles and, therefore, are not stored in bibliographic databases. Bowen suggests that the first step in finding data is to create an initial list of documents that are available (or that might be) and a list of initial sources.[179] Starting with these initial documents and sources, searching continues by iterating with analysis of the identified documents, so that the analysis indicates other documents for review, further questions to be asked, issues to be addressed, and references to be followed up on.[115,181] The next step is the creation of a database or document archive to maintain an inventory of identified documents from which to select a sample for in-depth analysis.[197,199] The third step is to categorise these documents in a way that makes sense for the review.

Creating initial lists of searching resources and key documents

Lists of initial documents (Table 5.4) and sources (Table 5.5) to search were drawn up, based on prior knowledge and drawing on material obtained from a course I participated in on medical device regulation (run by 'Clinical Research Development Ireland' (CRDI) in conjunction with Cúram, a national research centre focussing on the development of medical devices) to ensure their relevance.[201,202]

Table 5.4.Initial list of regulatory documents for the review

Document name or reference	Rationale
Council Directive 93/42/EEC	This is Medical Device Directive, the key piece of legislation underpinning the regulation of medical devices in the EU and in Ireland.
EN ISO 13485: 2016	This is the harmonised EU standard specifying the requirements of a Quality Management System (QMS) for medical device production
MEDDEV 2.4/1 rev 9	This provides guidance for the application of the classification rules set out in the MDD, (non-legally binding)
MEDDEV 2.7.1 rev 4	This provides guidance on conducting clinical evaluations as required by the MDD, (non-legally binding)
MEDDEV 2.12-1 rev 8	This provides guidance regarding the requirements of a vigilance system for medical devices (non-legally binding)
MEDDEV 2.12-2 rev 2	This provides guidance on the conduct of post-market clinical follow-up studies, (non-legally binding)
Council Directive 90/385/EEC	This is the Active Implantable Medical Device (AIMD) Directive (to restrict the focus of the review this won't be explored in depth)
EN ISO 14155 – Clinical Investigation of Medical Devices in Human Subjects: Good Clinical Practice	This is the harmonised EU standard specifying how good clinical practice in the conduct of clinical investigations should be attained
Helsinki Declaration	This states the ethical principles which the MDD requires clinical investigations to be conducted by.
EN ISO 14971:2012	This is the harmonised EU standard specifying the requirements regarding risk management of medical devices that allow presumption of conformity with the essential requirements of the MDD
Application forms to NSAI	These provide information on the implementation of the MDD
NBOG & GHTF documents	These indirectly provide information on the implementation of the MDD
SI 252 of 1994	This is the Irish Statutory Instrument which introduced and put into effect the MDD into Irish law
Medical Device Regulation (Regulation 2017/745)	This is the new Regulation that was introduced in 2017, which was meant to come into full force in May 2021, although this was deferred until the following May due to Covid-19.

To facilitate the searching process, the conceptual frameworks were used for creating questions, listed in Table 5.6, to guide the location and retrieval of relevant documents.

Table 5.5: Initial list of searching resources to review the regulatory process

Institution	Applicable level (EU, MS or Int)	Website
European Union	EU	https://europa.eu/european-union/index_en
European Parliament	EU	https://europa.eu/european-union/about-eu/institutions-bodies/european-parliament_en
European Commission	EU	https://europa.eu/european-union/about-eu/institutions-bodies/european-commission_en
Council of the European Union	EU	https://europa.eu/european-union/about-eu/institutions-bodies/council-eu_en
European Council	EU	https://europa.eu/european-union/about-eu/institutions-bodies/european-council_en
European Court of Justice	EU	https://europa.eu/european-union/about-eu/institutions-bodies/court-justice_en
Competent Authorities for Medical Devices (CAMD)	EU	https://www.camd-europe.eu/
Notified Body Operations Group (NBOG)	EU	https://www.nbog.eu/
Medical Devices Coordination Group (MDCG)	EU	https://ec.europa.eu/growth/sectors/medical-devices/new-regulations/guidance_en
Irish Government	MS	https://www.gov.ie/en/ https://www.oireachtas.ie/en/visit-and-learn/how-parliament-works/ https://www.oireachtas.ie/en/visit-and-learn/how-parliament-works/role-of-the-oireachtas
Irish judiciary	MS	https://www.gov.ie/en/organisation/the-courts-service/
Health Products Regulatory Authority (HPRA)	MS	https://www.hpra.ie/homepage/medical-devices
National Standards Authority of Ireland (NSAI)	MS	https://www.nsai.ie/
Advertising Standards Authority for Ireland (ASAI)	MS	https://www.asai.ie/
International Medical Devices Regulators Forum (IMDRF)	Int	http://www.imdrf.org/
Global Harmonization Task Force (GHTF)	Int	http://www.imdrf.org/ghtf/ghtf-archives.asp
World Health Organization	Int	https://www.who.int/medical_devices/safety/en/

At the level of Supranational intervention, the first question was ‘what international or supranational bodies seek to influence medical device regulation?’ Some organisations were already known, other organisations were chosen for the review because they were referenced in documents from the EU or were meeting agenda or minutes of the

aforementioned organisations, or when their relevance became apparent during the analysis.

At the level of State interventions, the searching process was informed by questions relevant to Coglianese's seven-step regulatory process,[143] whilst at the level of 'The Rules', the questions were essentially the same, but focussed more specifically on the MDD or MDR. Searching iterated with analysis and reflection.

Description of the Information sources

The main sources of information were the websites and databases of the regulatory institutions (primarily the EU legislative bodies) and the regulatory authorities established by the EU medical device legal framework. The European Union provides access to a wide range of other EU documents and records at: https://europa.eu/european-union/documents-publications/official-documents_en, including access to EUR-Lex, which houses the Official Journal of the European Union (OJEU or OJ). Additional sources included the websites of supranational organisations and institutions. EUR-Lex was the main source of documents for this review, and is described in more detail.

EUR-Lex

EUR-Lex is the EU database for EU law (all of which is published in the OJ), which is situated within the europa.eu domain[i] (https://eur-lex.europa.eu).[203] It contains twelve collections of legal documents, including EU legislation (Directives, Regulations and Decisions), treaties, preparatory documents for EU legislation, EU Court reports (Court of Justice, General Court, and Civil Service Tribunal), and EU case-law, amongst others. The database also contains links to the national laws of Member States (MS), and statistics regarding the numbers and types of legal acts introduced each year by the EU.[204]

Institutional websites

'Documents' were sourced from the websites of the supranational organisations and the regulatory authorities tasked with implementing the EU legal framework. These included information directly presented on the webpages of these websites and documents, reports, presentations, and guidelines published on their websites, as well as meeting agendas and minutes or outcome statements where they were available.

National Competent Authority Reports

National Competent Authority Reports (NCARs) are reports shared between the national competent authorities (NCAs) on devices that have come to their attention as having had

[i] Internet domains are discussed in greater detail in section 1.5.2.2. Ensuring authenticity.

serious adverse events that were either unanticipated (unexpected) or where the expected trend has changed (worsened). Each NCAR represents a single device type or device category, but several incidents. These reports are confidential and not available to the public. However, the EU publishes summary reports regarding the number of reports the NCAs have shared at the EU-level. These documents contain very little detail, but they currently are the only cross-EU source of data on adverse events. Over the years, these reports have been housed in different directorates of the EU, making them difficult to find, but they are currently under the remit of the Directorate General for Health and Food Safety (DG-Santé)[i].

Creating a database

The resulting collection of documents was saved in a folder in Dropbox, thus creating a document archive. These documents included legislation, European and international treaties, guidelines, technical or harmonised standards, statistics, reports, organisational charts, meeting agendas and minutes, attendance records, lobbying information, documents describing the regulatory process in the EU and Ireland, application forms, notices (to industry, patients, or healthcare professionals), training programmes, and webinars, as well as the documents created from regulatory website webpages.

Categorising documents

Documents were scanned for relevance to the research, and categorised according to their source, such as the organisation/institution or the country, and/or according to the step in the regulatory process and by the type of document, such as legal documents, webpages or databases. Categorising was an iterative process, organising the data continued throughout the study as the number and range of documents increased. Each main category was subcategorised (using folders), and where necessary, subcategorised again. For example, from thirty-three main categories, a key subcategory was ‘Legal documents’, which contained 28 subcategories, the most important of which were: **MDD development and amendments**; **MDR prep and amendments**; **New Approach**; and **New Legislative Framework**.

5.3.2.1. Selecting

In a QDA study, there are frequently large numbers of documents collected, but not all of these can be analysed. Therefore, there must be a selection process to identify those that are most suitable for answering the research question(s). Bowen suggests that, to

[i] It has not been possible to locate the NCARs summary report for 2021 and 2022, but it is possible to find those for 2007-2014 at this link: https://ec.europa.eu/docsroom/documents/12980
And those from 2015-2020 at this link: https://health.ec.europa.eu/medical-devices-sector/directives/market-surveillance-and-vigilance_en

Table 5.6. Questions guiding the searching process

Step in the regulatory process[i]		Guiding Questions
A	Regulatory Institution => Rule-making institutions in the EU	1. What bodies or institutions have responsibility for making the rules for regulating medical devices in the EU? 2. What is their organisational structure and make-up?
B	Regulatory Policy => Rule-making process in the EU	1. What type of 'rules' do they make? 2. What is the decision-making process for making rules? 3. Who can influence this decision?
C	Regulation => Rules, i.e. Legal framework for medical devices	1. What are the key 'rules' regulating medical devices in Ireland and the EU? (i.e. the specific regulatory instruments such as directives, regulations, guidelines, standards, etc.) 2. What are the core elements of the 'rule'? 3. How have these changed over time?
D	Implementation => Rule-enforcing bodies & their processes	1. How is the MDD implemented? 1. Who are the stakeholders involved in its implementation? 2. What are the steps that each of the stakeholders (regulators) must follow in order to implement and comply with the regulations?
E	Behaviour change => The steps that a manufacturer must take to market their medical device	1. What behaviours are expected to result? 2. What are the steps that each of the stakeholders (targets) must follow in order to comply with the regulations? 3. What are the steps in the CE marking process?
F	Intermediate outcomes => CE marking ➔ Market access ➔ Patient access	1. What potential indicators might exist to measure market access and patient access? 2. What data is available for these indicators? (Is it accessible?)
G	Ultimate outcomes => The goals of the regulation	1. What evidence would indicate changes in the level of trade in medical devices? 2. What evidence would indicate changes in the level of safety (including effectiveness) of medical devices?

be included in a QDA study, the documents must be relevant to the research question, authentic and credible, and he recommends that researchers also consider their fit with the conceptual framework guiding the research project.[179] Caulley points out that for each detail in a document to be credible the primary source (witness) must be 'able to tell the *truth*, *willing to tell the truth*, be *accurately reported*, and *independently corroborated*'.[181] Furthermore, being aware of what might be expected to be available in records or accounts of an event or phenomenon is also important to highlight or surface gaps in the evidence, for example when *'… certain matters have been given little attention or that certain voices have not been heard'*.[179]

[i] The focus of this review is patient safety, therefore, although the effect of medical device regulation on trade is relevant and interesting, particularly in Steps F and G, this was deemed to be out of scope.

Finally, when there are several documents addressing the same issue choices must be made when selecting which documents to include in the analysis. In choosing, Caulley suggests considering four factors – the timing of writing, purpose of writing, intended audience, and the author of the documents. The reliability of a document is increased if it is written close to the time of the event, written in confidence or for a small audience. Caulley proposes using these '*rules of precedence'* to guide the process of choosing of one document over another.[181]

Relevance

However, one of the challenges with regulatory documents is negotiating the vast quantity of relevant documents. Typically, a piece of legislation will refer to other legislation, making it necessary to also know and understand its contents to make sense of legislation under study.

Furthermore, legislation is not static and is frequently amended. This means that, for some pieces of legislation it is necessary to review the original version and an amended version. For example, of seventeen pieces of legislation referenced by the original MDD, seven have since been updated and referenced in the legislation amending the MDD, and five additional pieces of legislation are also referenced.

The main research questions were broken down into sub-questions according to the different levels and steps of the regulatory process, listed in Tables 5.6. Rather than excluding documents, selection involved identifying the most relevant ones first, interrogating those and then choosing the next most relevant documents or those appropriate for further interrogation to follow up on an analytic thread. This continued until the questions were answered or data saturation was reached (i.e. new information was superfluous, or beyond the scope of the study). This approach resulted in a large volume of relevant documents.

Authenticity and credibility

Typically QDAs include documents drawn from archives, organisational records, statistical reports, or specific collections of documents, with many obtained from reliable sources. However, the majority of the documents in a documentary analysis of regulatory processes are legal documents or information and documents sourced from institutional websites. This required alternative approaches to verifying authenticity and assessing their credibility.

The authenticity of relevant institutional websites was checked by verifying the website owner identity through the Internet Corporation for Assigned Names and Numbers (ICANN) Domain Name Server (DNS) lookup system, https://lookup.icann.org/en. The authenticity of EU legislation published after July 2013 was verified using CheckLex.[205]

[205–209] Legislation published before July 2013 was assumed to be authentic as it was obtained from EUR-Lex, on the EU-verified website[i]. Despite compiling many documents by extracting relevant webpages into a single document, most documents included in this review[ii] were legal documents, guidelines, standards, application forms, official statistics, and official descriptions of organisations or their regulatory policy and law-making procedures.

Regarding credibility, legal documents, guidelines, and standards were deemed to be 'credible' in the sense that they are/were truthful accounts of the regulatory requirements. Similarly, guidelines, standards, application forms, statistics and official reports sourced from authenticated official websites[iii], many of which were also signed and dated, were deemed to be credible representations of the specific organisation's position on a topic.

Regulatory rules of precedence

In describing his proposed rule of precedence, Caulley was referring primarily to documentary accounts of events. However, regulatory documents don't, generally, recount events, instead, they set out rules to be followed, making Caulley's rules of precedence less applicable to regulatory documents.

Furthermore, regulatory documents have a hierarchy of authority, in the sense that there is a greater obligation to comply with the requirements contained within some in comparison to others. For example, guidelines are not legal requirements, whereas rules contained in legislation are legally binding.

There are also differing levels of authority between different types of legislation. The EU institutions *'adopt regulations, directives, decisions, recommendations and opinions'* to fulfil its obligations under the treaties.[210, Article 288] According to the Treaty on the Functioning of the European Union (TEFU) Regulations *'shall have general application'*, are binding in their entirety, and directly applicable to all MS, so that, once enacted, they become the law for every EU country.[210] Whereas a legislative Decision, which is also binding in its entirety, is only applicable to those to whom it is addressed, usually to specific MS or specific institutions or organisations.[210] Directives on the other hand are not directly binding but must be transposed into national law in order to take effect. However, it is also possible to challenge national law in the European Court of Justice

[i] It is assumed that any false legal documents published before 2013 would have been detected and replaced by now.

[ii] The particular documents reviewed are listed at each relevant level/step in the Findings section.

[iii] Of note, the IMDRF website could not be authenticated using the WHOIS system, as the information is redacted to protect the privacy of the registrant. However, the documents obtained from the website are, for the most part, signed and dated, and the organisation remains active. Furthermore, EU guidance directs users of the MEDDEV guidelines to these GHTF/IMDRF documents for additional guidance, therefore, the documents obtained from this website were assumed to be authentic.

(CoJ) if deemed not compliant with the relevant directive.[211] Therefore, rulings from the CoJ may support or overturn national law.

Directives are binding *'as to the result to be achieved, …, but shall leave to the national authorities the choice of form and methods'*, that is they specify an end or goal to achieve rather than specifying the means to achieve it.[210, Article 288]The EU institutions may also issue Recommendations and Opinions, but these have no legally binding force. Each of these (underlined) is an 'act' that the EU may perform[i].

Thus, there is a hierarchy of 'power' to enforce authority, as illustrated in Figures 5.13-5.14.

Figure 5.11. Hierarchy of regulatory documents[ii]

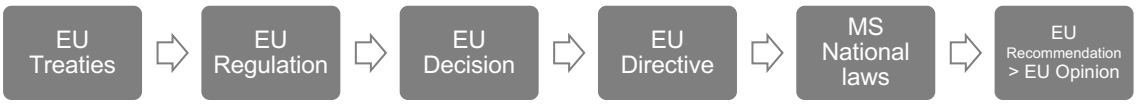


Figure 5.12: Hierarchy of legislative documents[iii]

Taking regulatory hierarchies into account as an additional factor for consideration, the rules of precedence were adapted for regulatory documents[iv], as shown in Figure 5.15. In this context, the 'reliability' of the regulatory documents is not so much that they express the 'truth', but rather, that they are more likely to represent what actually happens because of their level of authority or power to enforce the requirements. Where the contents are more specific, they may be more 'reliable' in the sense that it is clearer what should be done, but not that they are more likely to be adhered to, unless they are supported by effective enforcement mechanisms.

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[i] As will be shown later, the power to Act was originally conferred on the Council, but later treaties shared this power to act (i.e. to enact legislation) between the Council and the European Parliament, usually on foot of a proposal from the Commission. The Commission has no power to act in its own right, except in those cases where specific legislation confers this power through delegating power or conferring the right to enact implementing legislation. This right to enact implementing legislation empowers the Commission to introduce acts specifically to implement the original piece of legislation, whereas delegated power allows the Commission to make changes to the original piece of legislation. These delegated and implementing powers apply only to the aspects specified in the original legislation. These delegated and implementing acts may be in the form of Regulations, Decisions, or Directives.

[ii] Industry and professional codes of conduct express the types of behaviour that is expected of their members, but are mostly reflective of ethical standards rather than directions regarding how to perform tasks, and they are entirely voluntary.

[iii] Decisions are in between Regulations and Directives in that they have the same level of authority as a regulation, but with a reduced scope of application.

[iv] Note that timing is omitted from these rules of precedence, because, although timing is important, in general once published a regulatory document is effective, until such time as it is formally amended.

These rules guided the selection of documents, choosing the most relevant for a given step, the most authoritative, and the most reliable for the particular question(s) being addressed at a given level/step. However, for many of the steps, the preferred documents are deemed to be confidential and are not publicly available. Consequently, many of the documents included in the review do not fully comply with the rules of precedence, but were considered the best available sources of data at the time. Table 14.8 in the Appendices lists the key documents and some of the supporting documents according to each level or step selected for this review.

More reliable	>>> Reliability >>>	Less reliable
⇓	Documents written	⇓
Legislation > Standard Operating Procedure	←=====Rules=====→	Standards > Guidelines > Codes of Practice
Treaty > Regulation > Directive	←===Legislation===→	Recommendation > Opinion
To legislate or enforce	←====Purpose====→	To guide or advise
Regulators > Industry	←====Audience===→	Industry > Public
Intended for few eyes	←==========→	Intended for the public
Disinterested author	←====Author=====→	Vested interest
Nothing to gain/may lose by disclosure	←==========→	Something to gain by disclosure

Figure 5.13: Rules of precedence for regulatory documents

NCARs

Data were extracted from the summary reports on the NCARs shared by the EU and EFTA countries. The first report on EU NCAR data, covering 2007-2010, was published in 2011. Thereafter, reports were published annually. Data extracted from these reports included the number of NCARs per year and the numbers reported by each country (including non-reporters).

5.3.2.2. Appraising (making sense of)

Bowen refers to the next step as 'appraising' the documents, by which he means making sense of them – that is interpreting their contents to derive an understanding of their meaning and implications.[179] QDA, according to Bowen, is an iterative process that requires at least three levels of data interrogation.[179] Wesley recommends that the researcher becomes immersed in the data and puts it through a three-stage coding process.[198] Their recommendations differ slightly, with their proposed steps overlapping.

Additionally, Wesley recommends that the researcher takes steps to ensure the trustworthiness of the research as it is being conducted.[198]

I found that legislation was more complicated than plain English policy documents. It was necessary to become immersed in the documents to become familiar with them, and to understand what they were for, what they were actually saying (in plain English), and what they were doing or requiring, I found it was necessary to make connections between documents, identifying referenced legislation, reading the relevant sections, tracing its history back in time, and its development/amendment forwards.

Thus, there were four steps to the 'Appraising' stage for regulatory documents:

- Data immersion and familiarisation
- Tracking documents and their history
- Coding & Categorisation
- Ensuring trustworthiness

Data immersion and familiarisation

To familiarise myself with the documents I scanned their contents, reading those documents or parts of documents that appeared to be relevant or that later became relevant. This included the founding treaties and many of the subsequent treaties, the MDD and its amending legislation, the MDR and its amending legislation, and certain implementing legislation, as well as several MEDDEVs, GHTF/IMDRF guides, and MDCG guidance. I read and reread the MDD and MDR. I summarised information and extracted data into summary tables, and wrote notes in the margins of paper versions. I read them out loud and recorded my reading, and listened to the recordings. I created diagrams and summaries of the actors involved, and the implementation structures and processes, drawing on institutional or organisational websites and reports to supplement the legal texts.

Tracking documents and their history

I attempted to connect the different pieces of legislation, identifying and reading pertinent legislation referred to in the MDD, then reading the relevant sections of legislation referred to by that legislation, and so on. I sought and read amending and other cited legislation to develop an understanding of the legal history of the EU institutions and the legal framework for medical devices. I examined the descriptions in the treaties of the legal procedures that the institutions were mandated to follow in order to enact laws, creating diagrams to understand them. And I created timelines of events in tabular or diagrammatic form, to gain an understanding of potential influences on the legislative procedures.

Coding & Categorisation

Most documents were coded simply on paper, with notes in the margins and category codes. These were reflected on and I used writing as an analysis tool to gain insights. The rules in the MDD and the MDR were summarised in the margins and/or in Word and I extracted the MDD and MDR into Excel for coding and analysis[i].

I coded each rule according to whom it was addressed (the regulatory target), the requirement or rule, the conditions under which it applied, and referenced legislation. The rules were categorised into Economic Operators (focussing primarily on the manufacturer), MS (including their competent authorities), the Commission, and Notified Bodies (NBs) and I compared the legal requirements for each. I compared the conformity assessment procedures in the Annexes of the MDD by juxtaposing the requirements of each in a single sheet in Excel, which highlighted their similarities and differences and what was being required (or not) by each. I also examined and compared the requirements of the MDR with the MDD, in terms of their 'essential' or general safety and performance requirements, their conformity assessment procedures, clinical evaluation, and transparency/confidentiality, and clinical evidence requirements.

I summarised the reporting requirements for NCARs and conducted a simple quantitative analysis of the limited available data on serious AMDEs contained within the NCARs.

Research rigour - Ensuring trustworthiness

Research must be valid and trustworthy if it is to be useful. There are four accepted criteria against which to judge the trustworthiness of qualitative research, namely credibility, dependability, transferability, and confirmability.[126] These criteria are summarised in Table 4.1 together with Wesley's definition of each criterion.[198]

Wesley provides three strategies to attend to trustworthiness whilst the research is ongoing and proposes research approaches (summarised in Table 5.9) that may be used for implementing these strategies.[198] The three strategies are:

1. Triangulation[ii]

[i] I also chose the MDD and its amending legislation (five) to put through a three-stage coding process in NVivo, but I found this unwieldly, so I reverted to Excel, which made it easier to see the context of the particular rule being coded. I coded the MDR on paper. NVivo, a qualitative data management tool, was used in the hope that it would provide an explicit audit trail, as was 'reflexive journaling', however, the volume of material in these is prohibitively large with more than six years of notes and reflections recorded in Word documents, 20 copies, 6 notebooks, and 60 pages in a research journal in NVivo.

[ii] Triangulation refers to the use of 'multiple methods, sources, theories, and/or investigators' and the comparison of the findings across these different sources or approaches in order to strengthen the validity of the study's results.[212]

2. Intense exposure[i] and thick description[ii]
3. Develop an audit trail and attend to discrepant evidence[iii]

Additionally, Guba and Lincoln assert that to ensure trustworthiness researchers should provide access to the data to allow others to verify the findings, and provide an explicit description of the data interpretation process.[198, Guba and Lincoln, 1985, as cited in Wesley]

As far as possible, tabular summaries are presented of the methods and findings to bring clarity, an explicit description of the data interpretation process is provided, and access to the document archive and the evidence tables in Word and Excel can be made available. Additionally, Wesley's suggested approaches for achieving trustworthiness, and the strategies I used to enhance research rigour are summarised in Table 5.7.[198]

5.3.2.3. Synthesising

The earlier stages of coding represent the analysis, that is, the fracturing of the data to identify the elements within it, whilst the later stages involve the rebuilding of those elements into a more abstract form, an interpretation of the patterns observed in the data. This is the synthesis. Often this is a set of well-described themes or an explanatory or substantive theory addressing the research question.[115] Wesley recommends that researchers provide an interpretation that is plausible, makes sense, is supported by empirical evidence that explains the data '*as well or better than*' other interpretations,[198 p.10-11] and supplies sufficient evidence for and against alternative interpretations to allow readers to judge whether the researcher's interpretation might be better able to explain the data than the alternatives.[198]

[i] Intense exposure refers to immersion in the data or the study context so as to become intimately familiar with it. Thick description generally refers to the description of particular behaviours or actions happening within a particular social and historical context, that are described in sufficient detail and in such a way that readers have a clear picture of what is going on, 'hear' the participant's voice, can interpret the intentions, thinking, and motivation directing the behaviours described, grasp the relationships between participants, and experience emotion when reading the description.[213]

[ii] Ponterotto suggests that thick description should occur throughout the research report: in the methods section to clearly describe the study's sample and research procedures; in the findings section to present an adequate 'voice' for the study's participants and to understand the emotive and cognitive contexts of the actions described; and in the discussion section to merge the 'participants' lived experiences with the researcher's interpretations' to provide 'thick meaning' for the reader and to enable them to judge if they would have interpreted the data in the same way.[213]

[iii] An audit trail provides the evidence of the decisions that the researcher made during the analysis that led to the interpretations described. Attending to discrepant evidence serves to challenge and test any emerging conceptualisations or crystallising theories, so that it is possible to explore why discrepant cases or contexts don't fit the emerging concepts or theory, potentially uncovering important assumptions, and helping to either invalidate or to further refine the emergent concept(s), theme, or theory.

Table 5.7. Strategies I adopted to ensure research rigour

Trustworthiness criteria → Trustworthiness criteria for qualitative research	**Definition *Wesley 2010*[198]**	**Strategy taken to try to achieve each criterion**
Authenticity → Credibility (relates to internal validity or *'truth value'*)	*'a believable interpretation of the meanings'* in a document	Developing descriptive summaries of included documents, with quotes, then comparing my summary with other documents that interpret the originals. Also comparing these with information from key informants, and checking my understanding with experts when possible. Different sources and forms of documents were used in the analysis, (legal, administrative, and industry documents). Findings from the QDA were triangulated with findings from key informants (n=16). Different approaches to coding were used, which served as a means of theoretical triangulation, and the use of quantitative data (where available) served as a means of methodological triangulation.
Portability → Transferability (*'offers insights beyond the specific cases under study'* akin to generalisability*)*	*'broader applicability of the lessons drawn from their findings'*	By exploring the underpinning treaties, their goals and objectives, and their means of achieving them, the findings from the analysis may be relevant to other products with safety issues. By taking a European view, the findings are relevant to other MS besides Ireland. Intense exposure was achieved through prolonged immersion in the data[i], reading, note-taking, summarising, drawing diagrams, using matrices in Excel or NVivo to make comparisons, and constantly thinking about the data. Thick description was achieved by providing summary diagrams, summaries, extracts, and quotations or paraphrasing and referencing relevant points in the texts, together with extensive searching of underpinning or background legislation and other documents to supplement understanding, which was then drawn on to further explain the contents of the MDD and the MDR.[ii]
Precision → Dependability (*'reliability, … 'replicability'"*)	*'"Would I have reached the same general conclusions, given the opportunity to read the same set of documents under similar conditions?".'*	As this depends, to a certain extent, on the reader's interpretation, in order to ensure dependability my supervisors read multiple drafts of my findings, including several of the document summaries, and commented on them. To improve the dependability of the findings I have also provided a detailed description of the development of the legal framework.
Impartiality → Confirmability (*'relatively unprejudiced … findings that are reflective of reality as opposed to their own pre-determined beliefs'*, i.e. protecting against bias, relates to objectivity in quantitative research)	*'ensuring that their conclusions are drawn from the evidence at hand, as opposed to the predispositions of the researcher. The results of a QDA study are confirmable if the inferences drawn are traceable to data contained in the documents themselves, and if the preponderance of evidence corroborates those findings.'*	Open coding was used in the first cycle of coding of the MDD and its amendments in order to not be led by my biases. These open codes and their subsequently developed categories also served as a means to fact-check against themes emerging across the other documents. Multiple quotes and their references are also provided to support the patterns (themes) identified in the data and the subsequent explanations developed for those patterns. Tables in Excel and Word, and research journals were used to create an audit trail. Discrepant evidence was attended to by comparing evidence supporting the two main alternative explanations for medical device regulation – whether it was instituted in the public interest or private interests.

[i] I started this research in 2016

[ii] For example, to understand the conformity assessment procedures described in the MDD it was helpful to read the explanation provided in the Blue Guide and in the Notified Bodies Operations Group's (NBOG) Best Practice Guide entitled 'Certificates issued by Notified Bodies with reference to Council Directives – 93/42/EEC on medical devices (MDD) – 98/79/EC on in vitro diagnostic medical devices (IVDD) – 90/385/EEC on active implantable medical devices (AIMDD)' [214,215]. Summary diagrams have been extracted and presented as supporting materials.

A key objective of this research was to understand how the regulatory process operates to identify how it affects patient safety and how it can be improved. To address this objective a qualitative description of the process and the actors involved is more relevant than a purely thematic analysis. Furthermore, the regulatory process has changed and evolved over time, so that understanding a single point in time is less meaningful than understanding the history and current trajectory. Therefore, in addition to deriving themes and exploring potential explanations it is appropriate to provide a qualitative description of the findings and historical insights.

Qualitative Description

Thorne, Reimer Kirkham, and MacDonald-Emes suggest that it is better to wrestle with the material to gain an understanding of the whole by asking *"what is happening here?" and "what am I learning about this?"*, which, they argue, '*will typically stimulate more coherent analytic frameworks for interpretive description than will sorting, filing, and combining vast quantities of small data units'*.[133 p.74] Consequently, this approach was taken to analyse the bulk of the relevant documents to develop a macroscopic understanding of the regulatory process across its three levels. At the Supranational level the key actors were identified, and a summary of their stated goals or mission and means of achieving these is provided for each. Certain key documents produced by the most important of these Supranational organisations and their contents are described and analysed.

Timelines & History

At the State Intervention level the regulatory institutions and their regulatory policy were analysed using historical research methods, which Berg refers to as historiography, [216, p.210-22] in which past events are reconstructed from records and accounts, in this case legislation. Berg suggests that historiography studies the '*relationships among issues that have influenced the past, continue to influence the present, and will certainly affect the future (Glass, 1989)*', [216, p.211] Consequently, an historical narrative based on the relevant legislation and regulatory policies was developed.

Interpretive Description

I used qualitative description with '*hues'* of interpretive description to describe the regulatory rules interpretively to develop an understanding of how the regulatory process operates and its effects on patient safety and the evidence available for evaluating clinical outcomes [133,217, p.337].

Deriving themes

Through the steps and processes described above, patterns in the data and key issues affecting patient safety were identified and categorised thematically. Some of these themes emerged during the writing process (e.g. for the sections analysed using historiography), some during the search for and summarising of data, and others during the coding[i] process. Writing also served to develop the analysis and identified additional themes that were not identified through the coding process (e.g. regarding the regulatory institutions and their regulatory procedures), as well as highlighting assumptions that turned out to be false.[ii] These patterns were investigated further by questioning my assumptions, and reflecting on the identified patterns in the light of the findings from the substantive and theoretical literature on the regulation of medical devices.

Exploring possible explanations

The final stage of data interrogation involves examining what it all means, that is interpreting the data to explicate how it is perceived or how it may be understood, and the implications of this.[179]

I explored potential explanations for the themes identified in the data, drawing on Stigler's theories to guide my analysis, by asking[145]: Who benefits? Who bears the burdens? And What form does the regulation take? Furthermore, do the answers to these questions point towards public or private interest? I then sought for evidence that supported the alternative explanation.

Reporting

The findings from this study are subdivided into three findings chapters and the thesis discussion chapter. The regulators and their regulatory policy are described in Chapter 8. The EU medical device legal framework is presented in Chapter 9. The implementation of the EU legal framework and its effects are discussed in Chapter 10. The themes identified across these three chapters are discussed in the Thesis Discussion chapter, where they are juxtaposed with the findings from the review of lifecycle evaluation models and reflected on in the light of recent literature.

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[i] The coding and categorising processes described previously allowed data to be organised into categories and themes, which were visualised graphically in charts (and word trees), and organised in evidence tables (using Excel) enabling the development of themes.

[ii] An example of the first point are the two inter-related themes of power and legitimacy, which only became apparent during the narrative description of the development of the treaties and the EU institutions, whilst attempting to explain the trajectory of their development. An example, of the second point is that I had assumed that one of the difficulties that the MDD had in ensuring safe outcomes was that it was intended to fulfil two goals that were frequently competing, namely, to increase trade and to improve patient safety. However, as the analysis progressed it became apparent that safety was a trigger rather than a primary goal of the MDD, and in fact the primary goal was to improve trade, and safety was not in fact a competing goal but barely a goal at all.

6. A qualitative synthesis of lifecycle models used for evaluating medical devices

The research questions that this study sought to address were:

RQ1. What lifecycle approaches, models or frameworks have been used to evaluate medical devices?

a. What is meant by the 'medical device lifecycle' and 'lifecycle evaluation'?

b. How do these differences in meanings affect patient safety?

To answer these questions, the findings are presented in five sections, with a brief overview first to answer RQ1. The findings from the comparative analysis are then presented in a tabular and narrative format to describe the meanings attributed to 'lifecycle' and 'lifecycle evaluation' as embodied within the models, followed by the third section describing the model archetypes, which together answer RQ1.a. To answer RQ1.b, the fourth section describes the findings from the thematic analysis, with the assumptions underlying these themes and their implications for patient safety being discussed in the discussion section. Finally, the conclusions set out the key issues and potential solutions.

6.1. Overview

Fifty-two models were included in the synthesis, represented by fifty-one key texts, drawn from multiple different perspectives and organized into four broad categories for comparison. Nine models were derived from Healthcare (HC), sixteen from Policymaking (Policy), eight from Regulation (Reg), and nineteen from Trade and Industry (T&I). Table 6.4 lists the models, according to the year of first appearance, providing the **abbreviated names** that are used throughout this study to denote each model, and using colour to indicate their broad perspectives (*HC = green; Policy = yellow; T&I = orange; Reg = blue*). Grey font indicates that this was the earliest identified source of one of the included models, but it was not used as the key reference text.

The table highlights the fact that the earliest models originated from T&I and Policy, with Reg models appearing in 1986, more than half a century after the earliest model (1930) identified for this review, and with HC models only beginning to appear in the late 1990s.

Table 6.1. List of models included in the synthesis

Year 1st ref	Lifecycle model	Abbreviated name	Author/ Proposer	Ref(s)
1930	Product Life Cycle	**PLC**	Kuznets	218,219 220
1943	Acceptance and diffusion of hybrid corn seed in two communities in Iowa	**(RG-DOI) DOI**	Ryan & Gross	221,222
1960	Baldock New Product Development	**Baldock-NPD**	Baldock	223
1962	Life of an innovation	**DOI**	Rogers*	137
1965	Product Life Cycle	**PLC**	Levitt*	224
1969	The Bass Model	**Bass**	Bass	225,226
1979	Life history and routinization of an innovation	**IRP**	Yin	227
1981	7 stages: medical innovation career	**7Sm-IC**	McKinlay	76
1982	BAH model of product development	**BAH-NPD**	Booz, Allen & Hamilton	228,229
1982	Business Lifecycle (High-technology ventures)	**BLC**	Galbraith	230
1982	Product/Industry Life Cycle	**ILC**	Gort & Klepper	231,232 233
1986	New Product Development Process	**CK-NPD**	Cooper & Kleinschmidt	234
1987	A diffusion theory model of adoption and substitution for successive generations of high-technology products	**Norton-Bass**	Norton & Bass	235
1990	Stage-gate system	**SG-CK-NPD**	Cooper	236
1991	Technology Adoption Life Cycle	**TALC**	Moore	237,238
1994	Generalized Bass Model	**G-Bass-M**	Bass, Krishnan, & Jain	239
1995	Technology Readiness Levels	**TRL**	Mankins	240
1997	Product Development life cycle	**MDDP**	FDA	241
1997	A framework of iterative economic evaluation	**4S-IEE**	Sculpher, Drummond & Buxton	242,243
1997	VA Technology Transfer Process	**VA-NPD**	Sheredos & Cupo	244
1999	Total Product Lifecycle (TPLC)	**TPLC**	Feigal Jr. for the Institute of Medicine	245,246 247

1999	RE-AIM Framework	**RE-AIM**	Glasgow, Vogt & Boles	[248]
2001, authored 1999	Phases in the life span of medical devices	**MDLS**	Cheng	[249]
2003	Major phases in the life span of a medical device	**MDLS**	Cheng	[97]
2003	Healthcare Technology Life Cycle	**HCTLC**	Cheng	[97]
2004	A systems-based user-centred approach to healthcare design	**SUHCD**	Clarkson	[250]
2004	Conceptual Model for Considering the Determinants of Diffusion, Dissemination, and Implementation of Innovations in Health Service Delivery and Organizations	**DDDII**	Greenhalgh et al	[251]
2004	Technology adoption lifecycle Conceptual attractor & H Framework	**TALC-CAHF**	Meade & Rabelo	[252]
2005	Healthcare Technology Management Cycle	**(HTMC) ELC**	Temple-Bird et al	[102,253]
2009	Technology risk and readiness assessment framework	**IRM-TRL**	Mankins	[254]
2009	IDEAL Framework	**IDEAL**	McCulloch et al	[255,256 257]
2009	Industrial Emergence Framework	**IEF**	Phaal et al	[258,259]
2009	Medical device design & development stage-gate process	**SG-MDDP**	Pietzsch et al	[154]
2010	The Innovation Life Cycle	**IC+**	Croslin	[76260]
2010	Lifecycle of Technology	**TLC**	Mytton et al	[96]
2010	EAES guideline on methodology of innovation management in endoscopic surgery	**EIM-2DA**	Neugebauer et al	[261]
2011	New Product Development Framework	**Bhuiyan-NPD**	Bhuiyan	[262]
2011	Conceptual Framework of the University Spin-off Venturing Process	**USVP**	Rasmussen	[263]
2011	Medical device life-cycle	**MDLC**	Velazquez-Berumen	[103]
2012	Health Product Vigilance Framework	**HCanada-MDRegLC**	Health Canada	[264,265]

2013	The Innovation Cycle	**IC**	CIRAS	[266]
2013	The Innovation Cycle	**WW-IC**	Wright & Weinstein	[267]
2014	Project Life Cycle	**PrLC**	NASA	[268]
2014	The integration of risk management process with the lifecycle of MD software	**IRM-SaMDDP**	Pecoraro & Luzi	[269]
2014	Treatment 'lifecycle' framework	**RxLCF**	Provoost et al	[270]
2014	Life cycle of medical devices – Lifecycle approach to regulation & the importance of reporting incidents to the Therapeutic Goods Administration (TGA)	**TGA-MDRegLC**	Reeves & Garcia	[271]
2015	Equipment Life Cycle	**ELC**	Worm* (THET)	[102,253]
2016	Product Innovation Life Cycle	**PILC**	Baeyens	[272]
2016	IDEAL-D Framework	**IDEAL-D**	Pennell et al	[111,273] [112]
2017	Framework for Theorizing and Evaluating Nonadoption, Abandonment, and Challenges to the Scale-Up, Spread, and Sustainability of Health and Care Technologies	**NASSS**	Greenhalgh	[274]
2017	Health Technology Life Cycle	**HTLC**	Gutiérrez-Ibarluzea et al	[275]
2017	Optimal methodology for the introduction of new orthopaedic implants.	**OIM-DA**	Hannan et al	[276]
2017	New Health Technologies – Lifecycle for integration into healthcare systems	**nHTLC4I**	Paris et al	[277]
2017	Lifecycle of a medical device	**Swissmedic-MDRegLC**	Swissmedic	[278]
2018	Total Product Lifecycle (TPLC)	**FDA-MDRegLC**	FDA	[279]
2018	EUnetHTA's lifecycle approach	**EUnetHTA-MDLC**	Meyer, Brühl & Omstad	[280]

Colour coding used to indicate perspective: *HC = green; Policy = yellow; T&I = orange; Reg = blue*

6.1.1.1. Categorising models into broad categories

The next two tables show which of the four broad perspectives the models were assigned to in order to compare across perspectives.

Table 6.2. The broad categories to which the models were assigned

Trade & Industry (n=19)	**Policymaking (n=16)**
PLC(4)	*DOI*[137]
Baldock-NPD[223]	*IRP*[227]
Bass[225,226]	*7Sm-IC*[76]
BAH-NPD[228,229]	*TRL*[240]
BLC[230]	*4S-IEE*[242,243]
ILC[231–233]	*RE-AIM*[248]
CK-NPD[234]	*DDDII*[251]
Norton-Bass[235]	*IRM-TRL*[254]
SG-CK-NPD[236]	*TLC*[96]
TALC[237,238]	*MDLC*[103]
G-Bass-M[239]	*PrLC*[268]
TALC-CAHF[252]	*PILC*[272]
USVP[263]	*NASSS*[274]
IEF[258,259]	*HTLC*[275]
SG-MDDP[154]	*nHTLC4I*[277]
IC+[260]	*EUnetHTA-MDLC*[280]
Bhuiyan-NPD[262]	
IC[266]	
IRM-SaMDDP[269]	
Healthcare (n=9)	**Regulation (n=8)**
VA-NPD[244]	*MDDP*[241]
SUHCD[250]	*TPLC*[245–247]
ELC[102,253]	*HCTLC*[97]
IDEAL[255–257]	*MDLS*[97]
EIM-2DA[261]	*HCanada-MDRegLC*[264,265]
WW-IC[267]	*TGA-MDRegLC*[271]
RxLCF[270]	*Swissmedic-MDRegLC*[278]
IDEAL-D[111,112,273]	*FDA-MDRegLC*[279]
OIM-DA[276]	

Table 6.3. Models, with author names, according to their assigned category

Trade & Industry (n=19)	Policymaking (n=16)
PLC, *Levitt, 196*	***DOI,*** *Rogers, 1962*[137]
Baldock-NPD, *Baldock, 1960*[223]	***IRP,*** *Yin, 1981*[227]
Bass, *Bass, 1969*[281]	***7Sm-IC,*** *McKinlay, 1981*[76]
BAH-NPD, *Booz, Allen & Hamilton, 1982*[228]	***TRL,*** *Mankins, 1995*[240]
BLC, *Galbraith, 1982*[230]	***4S-IEE,*** *Sculpher, Buxton, & Drummond, 1997*[243]
ILC, *Gort & Klepper, 1982*[232]	***RE-AIM,*** *Glasgow, Vogt, & Boles, 1999*[248]
CK-NPD, *Cooper & Kleinschmidt, 1986*[234]	***DDDII,*** *Greenhalgh et al, 2004*[251]
Norton-Bass, *Norton & Bass, 1987*[235]	***IRM-TRL,*** *Mankins, 2009*[254]
SG-CK-NPD, *Cooper, 1990*[236]	***TLC,*** *Mytton et al, 2010*[96]
TALC, *Moore, 2001*[238]	***MDLC,*** *Velazquez-Berumen, 2011*[103]
G-Bass-M, *Bass, Krishnan, & Jain, 1994*[239]	***PrLC,*** *NASA, 2014*[268]
TALC-CAHF, *Meade & Rabelo, 2004*[252]	***PILC,*** *Baeyens, 2016*[272]
USVP, *Rasmussen, 2011*[263]	***NASSS,*** *Greenhalgh et al, 2017*[274]
IEF, *Phaal et al, 2009*[259]	***HTLC,*** *Gutiérrez-Ibarluzea, Chiumente & Dauben, 2017*[275]
SG-MDDP, *Pietzsch et al, 2009*[154]	***nHTLC4I,*** *Paris et al, 2017*[277]
IC+, *Croslin, 2010*[260]	***EUnetHTA-MDLC,*** *Meyer, Brühl & Omstad, 2018*[280]
Bhuiyan-NPD, *Bhuiyan, 2011*[262]	
IC, *CIRAS, 2013*[266]	
IRM-SaMDDP, *Pecoraro & Luzi, 2017*[269]	
Healthcare (n=9)	**Regulation (n=8)**
VA-NPD, *Sheredos & Cupo, 1997*[244]	***MDDP,*** *FDA, 1997*[241]
SUHCD, *Clarkson, 2004*[250]	***TPLC,*** *Feigal Jr. for the Institute of Medicine, 2010*[245]
ELC, *Worm (THET), 2015*[102,253]	***HCTLC,*** *Cheng, 2003*[97]
IDEAL, *McCulloch et al, 2009*[255–257]	***MDLS,*** *Cheng, 2003*[97]
EIM-2DA, *Neugebauer & Becker et al, 2010*[261]	***HCanada-MDRegLC,*** *Health Canada, 2013*[265]
WW-IC, *Wright & Weinstein, 2013*[267]	***TGA-MDRegLC,*** *Reeves & Garcia, 2014*[271]
RxLCF, *Provoost et al, 2014*[270]	***FDA-MDRegLC,*** *FDA, 2018*[279]
IDEAL-D, *Pennell et al, 2016*[111]	***Swissmedic-MDRegLC,*** *Swissmedic, 2017*[278]
OIM-DA, *Hannan et al, 2017*[276]	

6.1.1.1. Quality Appraisal Results

This section briefly describes the findings from the quality appraisal process. The QA results from the individual models are shown in Figure 6.9, whilst Figures 6.10-6.11 show the differences between the different perspectives[i].

[i] *Note:* The model described by McKinlay is the pattern that he has observed over the life of new health technologies, but not one that he recommends. Through it, he highlights how little evidence is available

Figure 6.9 summarises the QA summary scores, showing that almost half of the models scored zero, with almost a quarter scoring one or two. Just two models meet all three QA criteria, both of which derive from the Policy perspective (DDDII and NASSS, both by Greenhalgh and her teams).[251,274]

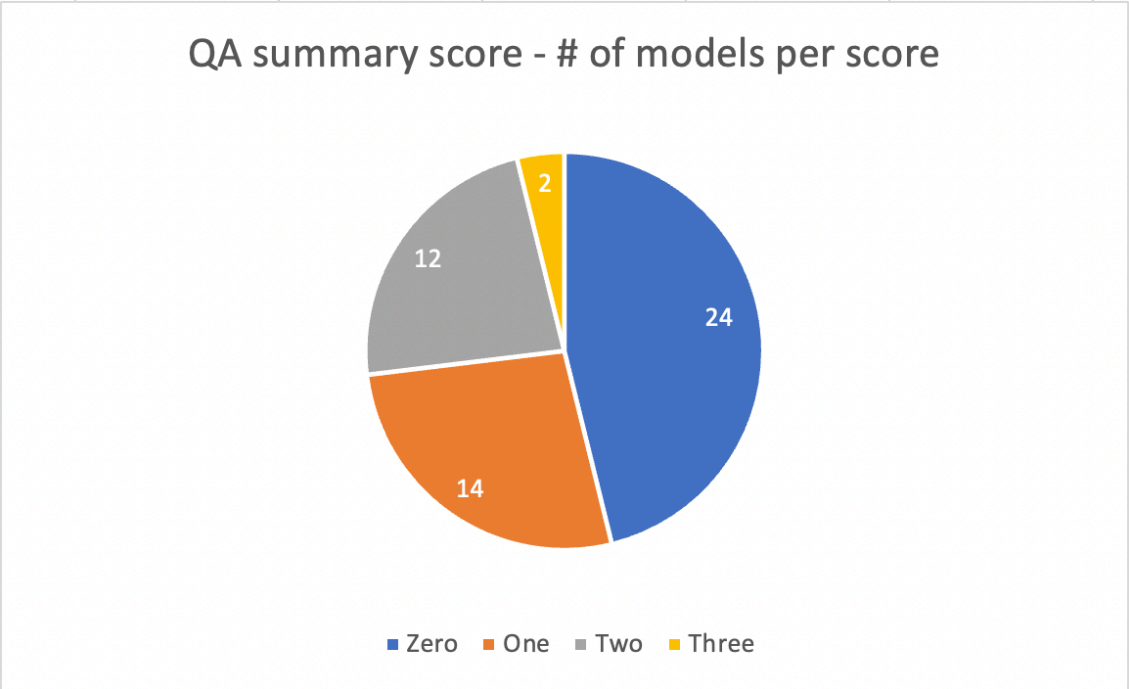

Figure 6.1. Summary of QA Summary Scores

Figure 6.9 shows the breakdown of QA scores across perspectives. It shows that, although none of the T&I models achieved a score of three, nevertheless, as a group they tended to score better than models from the other perspectives. It also shows that the Reg models scored particularly poorly, with seven out of the eight scoring zero, suggesting that there is little or no theoretical or empirical foundation to the Reg models. In contrast, the T&I models have stronger theoretical and/or empirical foundations than most other models. The Policy models have the widest spread of scores, but over half of them score zero. HC models also have a spread of scores, with slightly more than half scoring higher than zero. Thus, there is wide variability in the scores, but generally T&I have better QA scores, whilst Reg models as a group have the lowest.

for medical innovations when they are introduced, adopted by physicians, and later accepted as normal practice by the public and healthcare payers. He argues that this is bad for patients, payers, and healthcare. His model is intended to make us aware of the unacceptable level of evidence available for medical innovations. He then proposes an alternative – the assessment of population health needs and a thorough assessment of innovations regarding their safety, effectiveness, cost-efficiency, appropriateness, and equity of access prior to allowing them to be publicly funded. He effectively dismisses the lifecycle approach and instead calls for a comprehensive assessment of an innovation before it is allowed to be adopted widely. This is in contrast to all the other models, which are described so that they can be used (not dismissed) to guide strategic planning or specific activities.

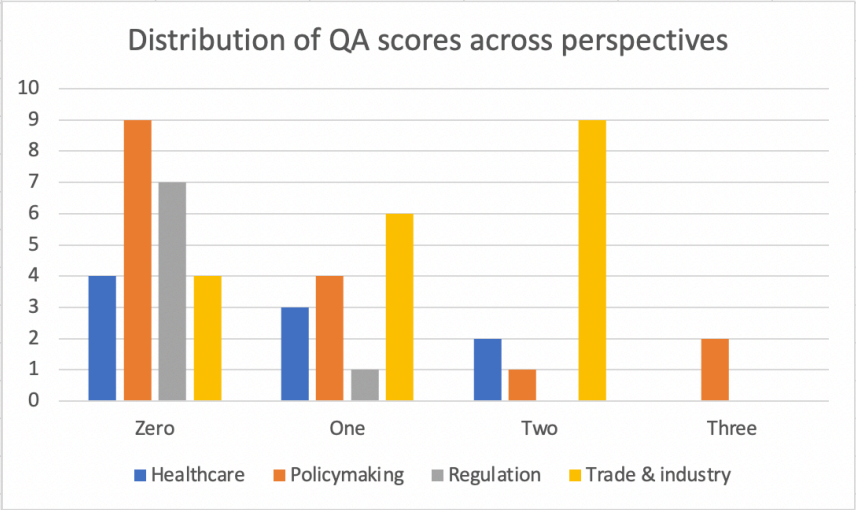

Figure 6.2. QA scores achieved by models from different perspectives

6.1. Comparative Analysis

My initial reason for conducting this review of lifecycle models was to identify a suitable framework for structuring an exploration of lifecycle processes. However, a common understanding of lifecycle evaluation amongst the clinical and HTA communities is that it means patient outcomes are evaluated across a device's lifetime, yet this is not what I observed in the models. So, it became clear that a more in-depth and interpretive analysis was required. Therefore, keeping patient outcomes, particularly safety, in mind, this comparative analysis explores what is meant by the 'medical device lifecycle' and 'lifecycle evaluation' as embodied meanings contained within the lifecycle models used by various actors and stakeholders involved in the life of a medical device. Much of this synthesis has been published in an article since I originally submitted my thesis for examination.[282]

Figure 6.12 illustrates the many dimensions across which the models varied, some of which I draw on in the following comparative analysis.

6.1.1.1. Medical device lifecycle[282]

There are different *forms*, *scopes*, and *types of process* used to represent the lifecycle of a medical device, described below.

The most common lifecycle *form* used is a linear series of stages (though iteration may occur) moving from the idea, through its development, growth, maturity, decline, to end-of-life (or a sub-set of these). A second form is a cycle of innovation, with each original invention being incrementally refined, which means that, for these models, the lifecycle encompasses several generations of a device. A third form is a pattern describing how a single lifecycle phase changes over time (e.g. sales or adoption), therefore, these models focus on how the parameter is affected rather than the effects the product has

on patients/end-users. In a sense, these are not actually device lifecycles, but they are, nevertheless, often what is meant by a device's lifecycle. Another set of models describe the lifecycle as movement through various levels in a system, and are, therefore, multi-level evaluations. For example, where a novel idea is developed into a technology, which becomes a component in a device, that is itself incorporated into a system (e.g. software developed for a switch, used in a mobile arm, which becomes a component in a robotic surgical device, such as the DaVinci Robot).[283]

In order to compare models' *scope* I drew on the Health Care Technology Lifecycle (HCTLC) model from the World Health Organization (WHO).[97, p.44] It illustrates the phases of the medical device lifecycle in terms of the activities/processes required across its lifespan. This includes seventeen specific stages of activity grouped into three phases – Provision, Acquisition, and Utilisation. Regulation may be considered as a separate process, but in this model, it is considered to be an integral part, where regulatory compliance is necessary for the device to transition to the next stage. The focus of interest during the provision stage is primarily on the new product development process, whilst the main focus of interest during the acquisition phase is on adoption or sales (i.e. diffusion). During utilisation the main focus of the models is on evaluating outcomes. However, whilst some models cover all of these phases and stages, in general, most cover only certain phases. In fact, Table 6.7 shows that the scope of the lifecycle models varied considerably across perspectives. For example, the T&I models cover only the provision stages, and approximately half of the Policy models do not include the utilisation stage, which means that these evaluation models do not examine (to any great extent) what happens after a device enters the healthcare system.

To compare the *types of process* embodied in the models, I used Van de Ven's process definitions, of which there are three: '*(1) a logic used to explain a causal relationship in a variance theory, (2) a category of concepts that refer to actions of individuals or organizations, and (3) a sequence of events that describe how things change over time'.*(19) Frequently, the models encompassed both the second and third of these definitions. However, approximately half of the models predominantly used a process definition that referred to actors' actions, a quarter referred to a sequence of events, whilst five used both. The majority of these were stage models, that is they described the lifecycle as distinct stages rather than as a continuous distribution of a particular variable. This contrasts with those applying the first definition, exploring causal relationships, all of which characterized the lifecycle quantitatively, and none of which focused on evaluating patient/end-user outcomes.

Author/Proposer, Year of publication	Empirical Data	Explicit literature review	Explicit Theory	*Model*
Baldock, 1960	X	X	X	*Baldock-NPD*
Rogers, 1962	√	?	√	*DOI*
Levitt, 1965	X	X	√	*PLC*
Bass, 1969	√	X	√	*Bass*
McKinlay, 1981	√	?	X	*7Sm-IC*
Yin, 1981	√	X	?	*IRP*
Booz, Allen & Hamilton, 1982	Unknown	Unknown	Unknown	*BAH-NPD*
Galbraith, 1982	X	X	√	*BLC*
Gort & Klepper, 1982	√	X	√	*ILC*
Cooper & Kleinschmidt, 1986	√	X	√	*CK-NPD*
Norton & Bass, 1987	√	X	√	*Norton-Bass*
Cooper, 1990	√	X	√	*SG-CK-NPD*
Bass, Krishnan, & Jain, 1994	√	X	√	*G-Bass-M*
Mankins, 1995	X	X	X	*TRL*
FDA, 1997	X	X	X	*MDDP*
Sculpher, Buxton, & Drummond, 1997	X	X	X	*4S-IEE*
Sheredos & Cupo, 1997	√	X	X	*VA-NPD*
Glasgow, Vogt, & Boles, 1999	X	X	√	*RE-AIM*
Moore, 2001	X	X	√	*TALC*
Cheng, 2003	√	X	?	*MDLS*
Cheng, 2003	X	X	X	*HCTLC*
Clarkson, 2004	√	?	√	*SUHCD*
Greenhalgh et al, 2004	√	√	√	*DDDII*
Meade & Rabelo, 2004	√	X	√	*TALC-CAHF*
Mankins, 2009	X	X	X	*IRM-TRL*
McCulloch et al, 2009	X	X	?	*IDEAL*
Phaal et al, 2009	√	X	√	*IEF*
Pietzsch et al, 2009	√	X	X	*SG-MDDP*
Croslin, 2010	X	X	X	*IC+*
Feigal Jr. for the Institute of Medicine, 2010	X	X	?	*TPLC*
Mytton et al, 2010	X	X	?	*TLC*
Neugebauer & Becker et al, 2010	X	√	√	*EIM-2DA*
Bhuiyan, 2011	X	X	√	*Bhuiyan-NPD*
Rasmussen, 2011	√	X	√	*USVP*
Velazquez-Berumen, 2011	X	X	X	*MDLC*
CIRAS, 2013	X	X	X	*IC*
Health Canada, 2013	X	X	X	*HCanada-MDRegLC*
Wright & Weinstein, 2013	X	X	X	*WW-IC*
Provoost et al, 2014	X	X	X	*RxLCF*
Reeves & Garcia, 2014	X	X	X	*TGA-MDRegLC*
Worm (THET), 2015	?	X	X	*ELC*
Baeyens, 2016	X	X	X	*PILC*
Pennell et al, 2016	√	X	X	*IDEAL-D*
Greenhalgh et al, 2017	√	√	√	*NASSS*
Gutiérrez-Ibarluzea, Chiumente & Dauben, 2017	X	X	X	*HTLC*
Hannan et al, 2017	√	?	?	*OIM-DA*
NASA, 2017	X	X	X	*PrLC*
Paris et al, 2017	X	?	√	*nHTLC4I*
Pecoraro & Luzi, 2017	X	X	√	*IRM-SaMDDP*
Meyer, Brühl & Omstad, 2018	X	X	X	*EUnetHTA-MDLC*
FDA, 2018	X	X	X	*FDA-MDRegLC*
Swissmedic, 2019	X	X	?	*Swissmedic-MDRegLC*

Figure 6.3. Quality Appraisal Results

Perspective	Healthcare	Policymaking	Economics & Industry	Regulation					
Model type	Theory	Model	Framework	Approach					
Model format	Diagrammatic	Graphical	Mathematical	List	Textual				
Data type	Continuous	Ordinal	Nominal/Categorical						
Purpose (focus on)	Define shape/trajectory	Factors affecting/affected	Identifying current stage	Deciding transition readiness	Actor's actions/activities				
Factors evaluated	Influencing factors	Characterising factors	Impacted factors						
Objective	Describe	Depict	Explore	Explain	Predict	Prescribe			
Unit of Analysis	Product	Person	Process	Chronology	Outcomes				
Characterisation	Quantitative – Amount or size	Qualitative – Stage of development	Mixed – Quantitative and qualitative						
Evaluative focus	Evidence	Efficacy	Risk	Safety	Approval	Sales	Uptake	Use	Other
Level of application (product)	Individual device	Collection of the same device	Type of device (non-proprietary)	Category	System				
Scope	Conception	Beginning	Development	Growth	Maturity	Decline	End-of-life		
Process definition	Event Sequence	Actions	Relationships (causal logic)						
Process theory	Lifecycle	Teleological	Evolutionary	Dialectical					
Direction of analysis	Retrospective	Contemporaneous	Prospective						
Timepoints	Single timepoint – whole lifecycle	Multiple timepoints – lifecycle stages	Repeated single timepoints						

Figure 6.4. An illustration of some of the different dimensions observed in the mod

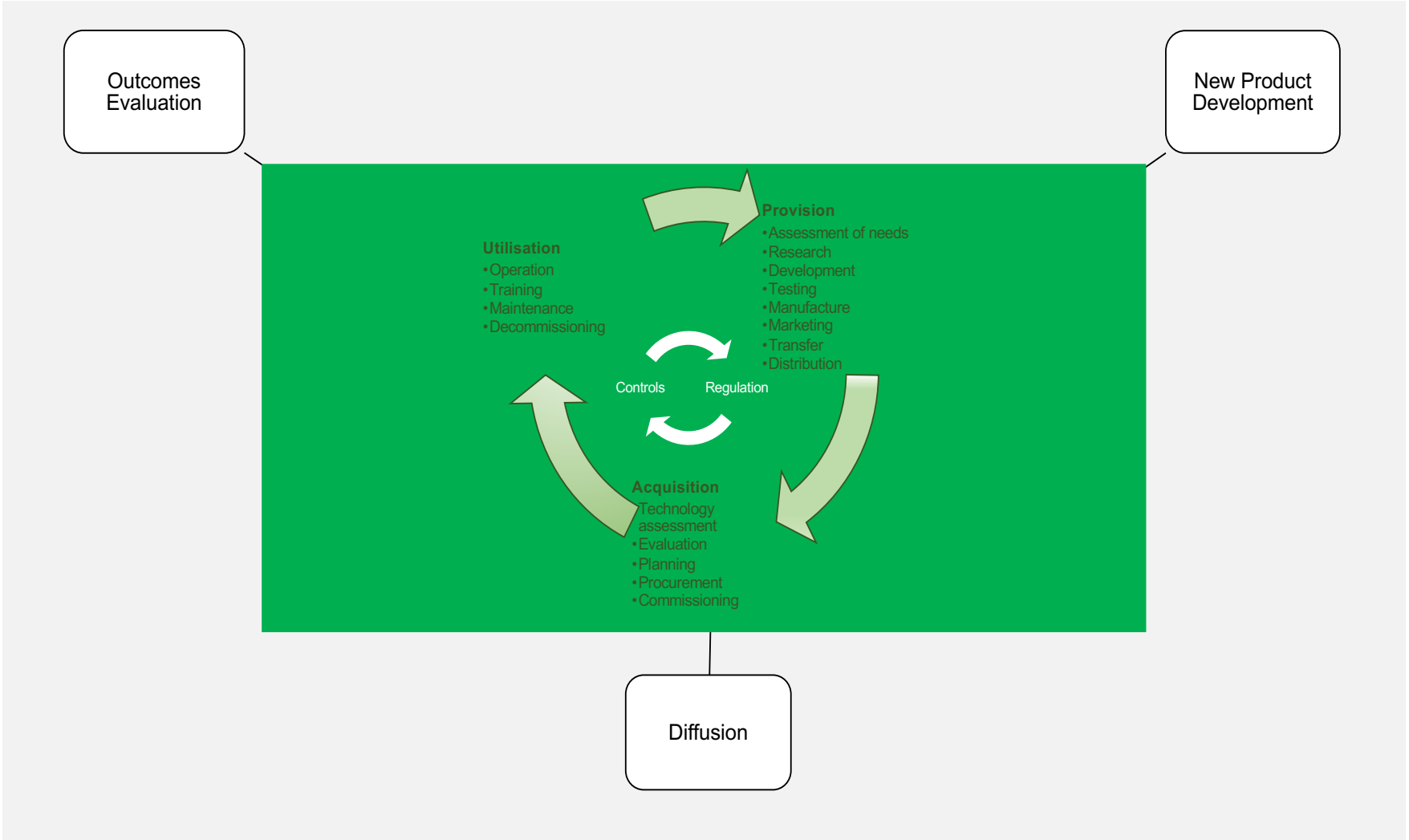

Figure 6.5. Illustrating the lifecycle scope

Table 6.4. Summary of Model and Study (reference text) Characteristics

Summary of Model Characteristics					
Device Type	**HC**	**Policy**	**Reg**	**T&I**	**Total**
Industry				2	2
Business				2	2
Product				7	7
Technology		3		2	5
Health Technology	1	5	1		7
Medical Device	4	1	7	2	14
Innovation	4	7		4	15
Lifecycle Type	**HC**	**Policy**	**Reg**	**T&I**	**Total**
A logic used to explain a causal relationship in a variance theory		3		4	7
A category of concepts that refer to actions of individuals or organisations	7	5	8	7	27
A sequence of events that describe how things change over time	1	6		6	13
Combines both a sequence of events that describe how things change over time and a category of concepts that refer to actions of individuals or organisations	1	2		2	5
Evaluation Type	**HC**	**Policy**	**Reg**	**T&I**	**Total**
Descriptive	1	8	4	2	15
Exploratory and/or Explanatory		3		3	6
Predictive		1		4	5
Prescriptive	8	4	4	10	26
Model Type	**HC**	**Policy**	**Reg**	**T&I**	**Total**
Framework	4	5	7	6	22
Model	5	8	1	13	27
Theory		3			3
Data Type	**HC**	**Policy**	**Reg**	**T&I**	**Total**
Qualitative	8	10	8	10	36
Quantitative		3		7	10
Mixed	1	3		2	6
1st Appearance of Model	**HC**	**Policy**	**Reg**	**T&I**	**Total**
1930-1939				1	1
1960-1969		1		2	3
1970-1979		1			1
1980-1989		1		5	6
1990-1999	1	3	2	3	9
2000-2009	3	2	2	4	11
2010-2019	5	8	4	4	21
QA Score	**HC**	**Policy**	**Reg**	**T&I**	**Total**
0	4	9	7	4	24

1	3	4	1	6	14
2	2	1		9	12
3		2			2

Summary of Reference Study Characteristics					
Publication Period	**HC**	**Policy**	**Reg**	**T&I**	**Total**
1960-1969		1		3	4
1980-1989		2		5	7
1990-1999	1	3	1	2	7
2000-2009	2	2	2	4	10
2010-2019	6	8	5	5	24
Geographical Region	**HC**	**Policy**	**Reg**	**T&I**	**Total**
Americas	2	8	4	15	29
Australia	1		1		2
Europe	3	5	1	3	12
International	3	3	2	1	9
Publication Type	**HC**	**Policy**	**Reg**	**T&I**	**Total**
Journal article	8	9		12	29
Academic publication		1			1
Conference/Presentation		2	1	2	5
Regulatory guidance			2		2
WHO Guidance		1	2		3
Book		3	1	3	7
Magazine				1	1
Online resource	1		1		2
Website			1	1	2
Funding/support or Conflicts (COI) declared	**HC**	**Policy**	**Reg**	**T&I**	**Total**
Funding/support declared	5	9	4	6	24
Personal interests stated				2	2
Writing support acknowledged		1			1
Disclaimer			1		1
Declared no COI	2	1			3
None declared	2	5	3	10	20
Uncertain				1	1
Total	**9**	**16**	**8**	**19**	**52**

Abbreviations: HC = Healthcare; Policy = Policymaking; Reg = Regulatory; T&I = Trade and Industry; NPD = New Product Development

6.1.1.2. Lifecycle evaluation

As shown in Tables 6.4 above and 6.5 below, lifecycle evaluation differs in terms of *what* gets evaluated, *when*, *how*, and *why*.

What is evaluated depends on the model's vintage and the stakeholder's goal.[i] Newer models focussed on describing the lifecycle or exploring factors that influence it. Older models were also used for these purposes, but several were also further developed for predictive and prescriptive purposes. Five broad purposes were identified and are listed in Table 6.9. However, most commonly, *what* is evaluated are the factors that are used to characterise the lifecycle, indicators of lifecycle progression, factors influencing the lifecycle trajectory or that are affected by it, and/or the outcomes from deploying a technology. However, relatively few of the models, and none of those from the T&I perspective, focus primarily on evaluating patient/end-user outcomes.

The *when* relates to the timing of evaluation, which may be a once-off event encompassing the entire lifecycle in a single evaluation (e.g. using empirical data to describe the sales/adoption pattern over time or by evaluating different lifecycle stages at a single point in time, either retrospectively using existing data or prospectively using modelling techniques) or it may be a lifecycle evaluation by virtue of the fact that the evaluation is repeated at several time points across the life of a technology. It is this latter type of evaluation that is generally considered to be a 'lifecycle approach' by the clinical and HTA communities.[61] However, twenty-two of the models included in this synthesis did not take this approach.

How the lifecycle is evaluated depends on the particular purpose of a given model. It may be performed using quantitative, qualitative, or mixed types of data, to conduct a descriptive, explanatory, predictive, or prescriptive evaluation. Table 6.9 shows that the most frequent purpose of evaluation is to define particular actions or activities that need to be undertaken at the different lifecycle stages, only fifteen of which describe approaches to evaluating end-user or patient outcomes.

[i] When examining the models and how they evolved over time, it became clear to me that these also have a kind of lifecycle, in that when a lifecycle is first mooted it is usually as a way of describing an observed pattern, generally, this is then validated empirically. Thereafter, it is explored to identify influencing or explanatory factors, subsequently, developing approaches to influencing the lifecycle trajectory, identifying where in the lifecycle an entity is, and predicting how it might proceed into the future. All of which are used to inform or influence strategic actions/activities for achieving a particular goal.

Table 6.5. Summary of Findings Table

Summary of Findings					
Purpose	**HC**	**Policy**	**Reg**	**T&I**	**Total**
Describe the lifecycle		3		4	7
Explore Influencing or impacted factors		3		3	6
Identify lifecycle stage	2			1	3
Determine readiness to progress	1	2		2	5
Define actions or activities	6	8	8	9	31
Audience	**HC**	**Policy**	**Reg**	**T&I**	**Total**
Trade & Industry		4	3	19	26
Policymakers	1	12	2		15
Regulators	1				1
Healthcare	7	2	1		10
General public			4		4
Totals for Audience	9	18	10	19	56
Characterized in terms of …	**HC**	**Policy**	**Reg**	**T&I**	**Total**
Development (pattern)				2	2
Development (stages)	8	7	8	10	33
Adoption (pattern)		9			9
Sales (pattern)				7	7
Health technology management activities	1				1
Outputs (Detailing …)	**HC**	**Policy**	**Reg**	**T&I**	**Total**
What happens	1	2	1		4
Influencing factors		3		8	11
‘How to’	1	2		9	12
Process/outcomes evaluation methods or activities	7	7		2	16
Regulation		2	7		9
Timing	**HC**	**Policy**	**Reg**	**T&I**	**Total**
Lifecycle evaluation at a single point in time		2	1	7	10
Separate evaluation of different phases at a single timepoint	1	5		6	12
Repeated evaluation at each lifecycle stage	8	9	7	6	30
Scope – Lifecycle	**HC**	**Policy**	**Reg**	**T&I**	**Total**
Provision			1	19	20
Acquisition	1	2			3
Utilisation		1			1
Provision & Acquisition		4			4
Provision & Utilisation			6		6
Acquisition & Utilisation	2	3			5
Provision & Acquisition & Utilisation	6	6	1		13
Scope – Devices	**HC**	**Policy**	**Reg**	**T&I**	**Total**
New	8	14		17	39
Established	1			1	2
All		2	8	1	11
Model Archetypes	**HC**	**Policy**	**Reg**	**T&I**	**Total**
NPD			1	10	11
Diffusion	1	7		9	17
Outcomes Evaluation	6	5			11
Hybrid	2	4	7		13
Total	**9**	**16**	**8**	**19**	**52**

Abbreviations: HC = Healthcare; Policy = Policymaking; Reg = Regulatory; T&I = Trade and Industry; NPD = New Product Development

Purposes and Goals

Another way of comparing lifecycle evaluation is to consider what the overarching goals are and the decisions that the models and their evaluations are intended to inform.

Goal or purpose is a multi-level concept, that may refer to, and includes, narrowly specific objectives, broader targets, key purposes, aims, and overarching goals. The terms are frequently used interchangeably, making their differentiation and expression of meaning more difficult. Therefore, for the purposes of this research, I have conceptualised them as a hierarchy, depicted in Figure 6.6[i], with the most specific being an objective, and the meaning growing increasingly broader as it moves to the outermost sphere, which is the ultimate or overarching goal. As can be seen, purpose is considered more specific than an aim or goal.

Therefore, the purposes listed in Table 6.5 are intended to serve a higher-level goal. What that goal is depends on the actor's perspective. The next four subsections describe the goals and key decisions of the four different perspectives and the evidence being sought for these.

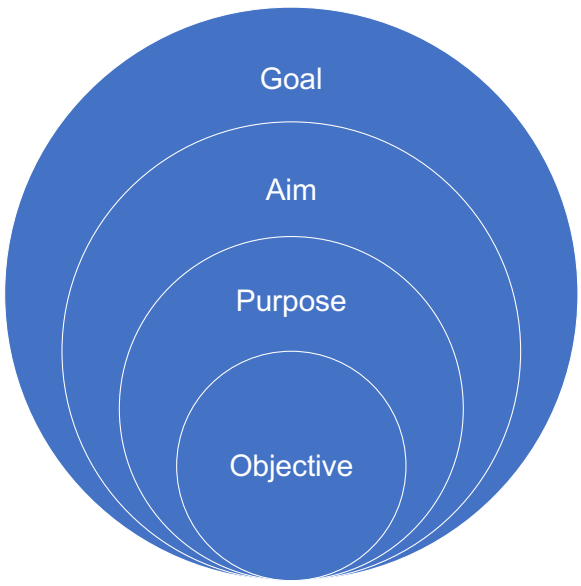

Figure 6.6. The multi-level nature of 'purpose'

[i] There may be more than four levels of goal or purpose, but this schematic seemed sufficient for this research.

Healthcare

The goal of healthcare is to provide safe, effective, efficient, appropriate, and affordable healthcare to those who need it. Healthcare decisions involve choosing the best device to use for a given patient with a particular condition at the right time, which means assessing whether the device is likely to be safe and effective for an individual patient, and whether it is the best choice of the available options for them at that time. This decision requires valid evidence of safety and efficacy (and/or comparative effectiveness). This is what the HC models attempt to achieve, either by advocating for the generation of the needed evidence or the evaluation of existing evidence, and providing guidance for one or other of these, or both. For example, '*The board of the European Association of Endoscopic Surgery (EAES) felt that evidence-based recommendations were needed for the safe introduction of innovative surgical devices and therapeutic or diagnostic procedures. The resulting guideline should give advice on ''when to do what'' when implementing innovations in the field of surgery.*'[261, p.1595] The authors of the IDEAL framework believed that '*By identifying many issues related to surgical research and deconstructing them into constituent methodological parts, we targeted several important areas to develop guidance for appropriate, evidence-based surgical practice.*'[255, p.1097]

However, the adoption of the advocated approaches appears to be slow.[284] Furthermore, recent research suggests that the quality of the evidence underpinning medical devices at market entry, and even at the point of initial reimbursement, remains largely unimpacted by these efforts.[31,285]

Policymaking

Policymakers often have dual policy goals – to promote trade and industry and to ensure that high quality and cost-effective healthcare is provided to the population for whom they are responsible. Thus, their decisions depend on the policy goal, but generally relate to supporting industry, regulating markets, and allocating resources. Sometimes, however, these goals are conflicting, since easing access to healthcare markets for trade and industry usually means reducing the quality and quantity of evidence required for market access, which reduces the evidence available for evaluating health technologies for their cost-effectiveness. *'Tension can arise between these objectives. Expediency must be balanced against adequate rigour, affordability with access. Aligning regulatory objectives with broader economic and industrial policy (e.g. to promote innovation, employment, growth, export and trade) may result in tension with goals of managing costs. In addition, each objective will be prioritised differently by stakeholder groups, adding a political dimension to the process.'*[286, p.118]

These decisions require different evidence. Therefore, from a trade policy perspective clinical evidence is required only insofar as it supports trade objectives. Unfortunately, the RCTs needed to establish the efficacy and safety of a medical device are costly and time-consuming, which means that they are viewed as burdensome to industry. In particular, the regulation of healthcare products is frequently viewed as a burden to industry rather than a protection for patients. '*The question is asked? What regulatory burdens are required to bring new products to market? But I like to rephrase the question: The regulations are not the primary mission of the FDA. The FDA laws are for consumer protection. So the question should be rephrased: What consumer protections are required to bring new products to market?*'[287, slide 5]

Amongst the sixteen Policy models included in this study, ten addressed healthcare policy objectives and six addressed trade or industrial policy. Furthermore, regardless of whether it is trade or healthcare policy that is being addressed, Policy models focus on gathering or generating evidence to meet one or more of three main objectives – the improvement of innovation development, the promotion of its uptake, and ways of evaluating its safety and/or effectiveness. However, even amongst those models addressing healthcare policy, only five focussed on evaluating clinical outcomes, which means that only these were seeking clinical evidence.

Trade & Industry

The goal of businesses is to increase their profits and market share. To do this they must make profit from the devices they sell and sell more of them than their competitors. Their decisions relate to investment and marketing strategy – they must decide which devices to continue to develop and bring to market, which to abandon, and how to successfully market those devices that they do bring to market. '*Following this process of information gathering and evaluation can lead to improved new product decisions on the part of firms by limiting the level of risk and minimizing the resources committed to products that eventually fail*.'[262, p.748]

They also need to know what factors influence the buying behaviour of their customers[i] and what strategies are most likely to be successful for marketing their device. '*In each case, the key to success is to focus in on the dominant "adoption type" in the current phase of the market, learn to appreciate that type of person's psychographics, and then adjust your marketing strategy and tactics accordingly.*'[238, p.20]

Thus, the evidence being sought is mostly not clinical evidence. However, some clinical evidence is required to gain access to regulated markets and to secure public

[i]This includes procurement and clinicians using the devices, but for implants, patients usually have no say in the purchasing decision.

procurement, though this may not include RCTs. '*A regulatory risk assessment and preliminary clinical plan assesses whether the approval process will require clinical trials.*'[154, p.021004-9]

Regulation

Medical device regulators are responsible for deciding whether a device may be legally placed on the market in their jurisdiction and the question that they ask is '*What consumer protections are required to bring new products to market?*'[287, slide 5]. The explicit goal for those from the Reg perspective is not, as is frequently assumed, to ensure that medical devices entering the market are safe and effective,[103] but rather that the regulatory requirements of their particular jurisdiction are met. '*Pre-market control is performed on the device to ensure that the* ***product*** *to be placed on-market complies with regulatory requirements*'.[97, bold in original] This means that the required evidence depends on the specific jurisdictions' regulations. The safety and effectiveness of medical devices at market entry depends on whether the regulations require this evidence or not.

In some jurisdictions this *sometimes* involves a market authorisation process, where the products can only be placed on the market if authorised by the regulators (e.g. in the US and Canada) usually on the basis of evidence of safety and effectiveness[i], but not always. *'… the premarket notification, or 510(k), process is a classification process, whereas PMA [Pre-market Approval] is a determination of safety and effectiveness that leads to approval. … For the 510(k) process, devices are <u>cleared</u> for marketing, not approved, and devices may not be marketed as "approved by FDA."*[288, p.12-13, emphasis in original] In other jurisdictions (e.g. Australia, European Union (EU), Switzerland) market authorisation is not required, instead, manufacturers of medium/high-risk devices must apply for an assessment of their conformity with the legal requirements by an external body, a conformity assessment body (CAS).[278] If the CAS deems them to be compliant, it authorises them to affix a marking (e.g. the CE marking in the EU) on their device that indicates that it is legally compliant. This is not the same as market authorisation, *'Unlike medicinal products, medical devices do not undergo an official authorisation procedure. For these devices, Switzerland follows what is specified for the European Union (EU) system of compliance assessment and certification, based on bilateral agreements. Compliance with internationally valid norms is evaluated by private entities.'*[278] This marking is required to legally market medical devices in the specified jurisdiction.

[i] The US and Canada require evidence of effectiveness, whilst Australia, New Zealand, and Switzerland require evidence of device performance, at least insofar as they are willing to accept the CE marking, which is based on (limited) evidence of safety and performance.

Regulatory models differ, but for the most part, regulators endorse the guidelines of the Global Harmonisation Task Force and follow the approaches, illustrated in Figure 6.7, suggested by WHO.[97] It shows that the evidence required by the regulators is made available to them via a technical dossier, quality system (QS) documentation, and audit in the pre-market phase[i], with PMS providing evidence in the post-market phase.

6.1. A Model Typology

Based on the primary focus of interest of the models I identified three model archetypes – the new product development (NPD), diffusion, and patient/end-user outcomes evaluation model archetypes, with a hybrid category for models where the primary interest covers more than one of these aspects[ii]. Therefore, the models were categorised and compared according to these archetypes as shown in Table 6.6.

6.1.1.1. New Product Development (NPD) models

In simple terms, the goal of NPD models is to improve the NPD process, to more efficiently develop commercially successful products. Their primary focus, therefore, is on the development process, not on ways of evaluating patient/end-user outcomes. Success for these models is about producing commercially lucrative products, therefore, their focus is not primarily on producing clinically effective devices. *'Factors that are necessary and guarantee commercial success are termed as critical success factors (CSF): … In fact, it is even suggested that NPD itself is a CSF for many organizations. … The challenge is to design a process for successful product innovation - a process whereby new product projects can move quickly and effectively from the idea stage to a successful launch and beyond.'*[262]

In fact, Teixeira, Bradley, and Teixeira[iii] argue that '*the main objective of any business is to make money*'.[289, p.9] They suggests that engineers '*have not been hired to make the longest lasting, strongest, most cosmetically pleasing medical device. They have been hired to make a medical device that is safe and effective for the application for which it is intended to be used. More important, they have been hired to do this and generate the most profit*.'[289, p.9] They further argue that *'the prime design criterion is whether the device will make money*'.[289, p.10]

[i] The contents of the technical dossier are confidential, as are the findings from the examination of the manufacturer's QS and from the audit of their premises.

[ii] Models were assigned to a hybrid group when their focus was relatively equally spread across two or more of the three archetypes, but if their focus was predominantly on one rather than the other then it was assigned to that type.

[iii] They detail yet another NPD model not included in the synthesis as it is similar to those included.

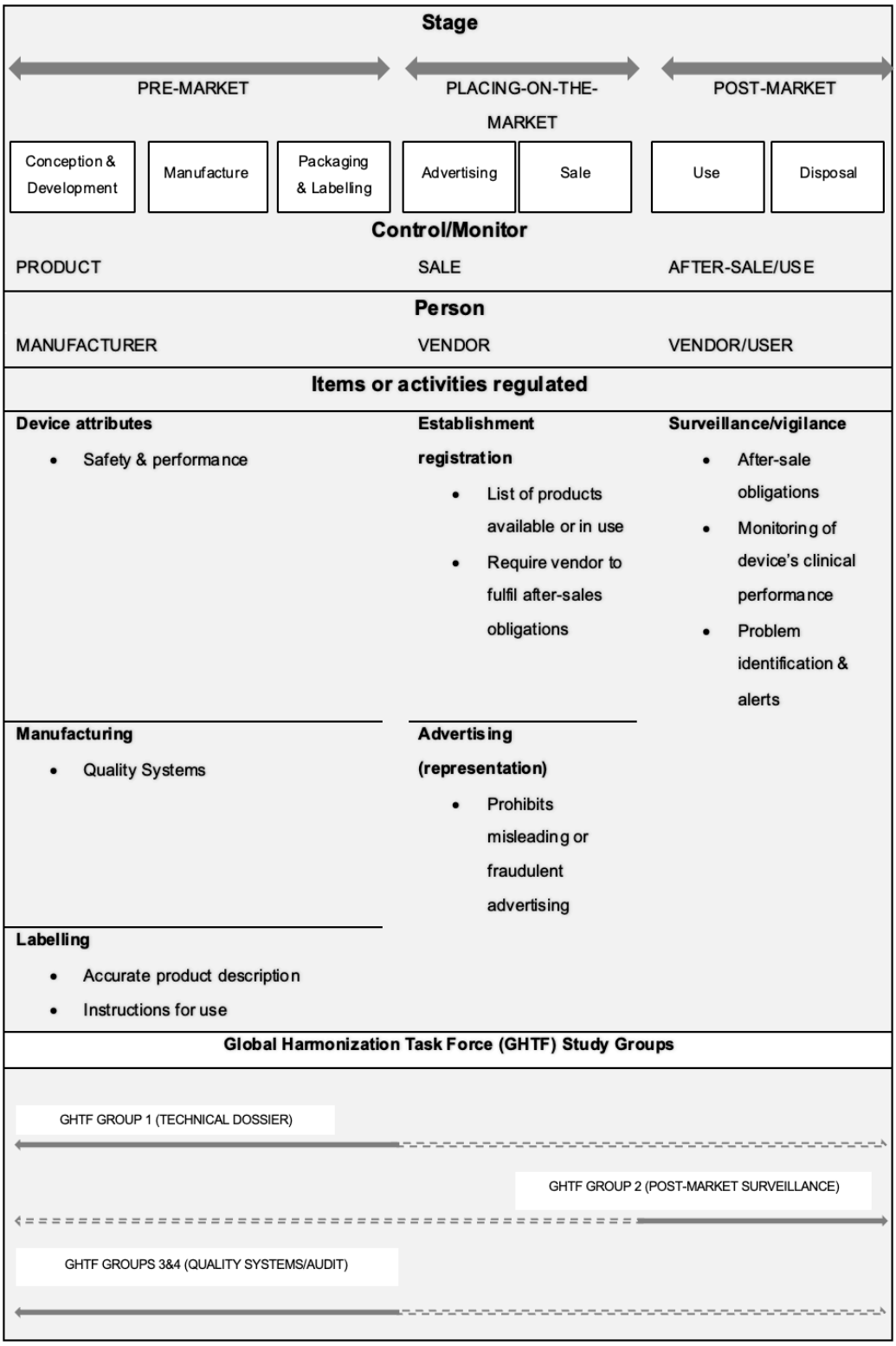

Figure 6.7. The Medical Device Life Span (MDLS) and the regulatory controls applied to the phases and activities requiring regulation (compiled from WHO/Cheng 2003)[97]

6.1.1.1. Diffusion models

The goal of Diffusion models is to improve the diffusion process, usually by increasing uptake of the technology. '*How can we spread and sustain innovations in health service*

delivery and organization?'[251, p.581] However, adoption is simply the demand side of diffusion, and some models focussed instead on the supply side of diffusion (i.e. sales). Regarding sales, Moore's model suggests that '*the way to develop a high-tech market is to work the curve left to right, focusing first on the innovators, growing that market, then moving on to the early adopters, growing that market, and so on, to the early majority, late majority, and even to the laggards. In this effort, companies must use each "captured" group as a reference base for going on to market to the next group. Thus, the endorsement of innovators becomes an important tool for developing a credible pitch to the early adopters, that of the early adopters to the early majority, and so on*.'[238, p.10] This demonstrates that many of the lifecycle models are intended to increase diffusion, whether by pushing or pulling the adoption of new technologies. These models do not provide a means of evaluating patient outcomes from the health technologies, but rather gather or generate the information needed to push/pull their adoption.

6.1.1.2. Outcomes Evaluation models

Outcomes Evaluation models are focussed on evaluating patient outcomes, mostly with a view to only allowing beneficial health technologies to become widely adopted: *'Uncontrolled diffusion of new health technologies in surgery, however, may lead to problems and harm to the patient (e.g., increased complication rates), especially during the introduction of a new technique or technology. It is common sense that the duty we owe to patients should never be diluted by any other goals. For the patient, the most important criteria of an innovation are safety, efficacy, and effectiveness.'*[261, p.1595]

The IDEAL framework was developed for surgical innovations because it was recognised that there is little regulatory control over the diffusion of innovative surgical procedures. Whilst the IDEAL Colloquium doesn't advocate for a regulatory system for these, they argue that new surgical procedures should not be adopted without appropriate evidence of their safety and efficacy, providing recommendations for stage-specific study designs for evaluating the safety and efficacy of a novel procedure. '*IDEAL is a framework for evaluations of surgical innovations, which follow a distinct development pathway differing from the approach developed for pharmaceutical interventions.*'[290]

6.1.1.3. Hybrid models

The Hybrid models are generally about controlling the NPD and diffusion processes, although four of these models have a combined focus on outcomes evaluation together with the NPD (SUHCD, VA-NPD, PrLC) or the diffusion (MDLC) process. None of the T&I models fell into this Hybrid category, whilst all but one of the Reg models did.[i]

[i] The regulatory models could possibly be assigned to a type of their own, but I chose not to, because their focus is on controlling the NPD and diffusion processes.

Table 6.6. Models categorised according to their Archetypes

NPD	Diffusion	Outcomes Evaluation	Hybrid
MDDP	ELC	OIM-DA	SUHCD*
IRM-SaMDDP	NASSS	IDEAL-D	VA-NPD*
Baldock-NPD	nHTLC4I	RxLCF	IRM-TRL
IC	DOI	WW-IC	TRL
USVP	IRP	EIM-2DA	PrLC*
Bhuiyan-NPD	7Sm-IC	IDEAL	MDLC*
SG-MDDP	PILC	EUnetHTA-MDLC	Swissmedic-MDRegLC
BAH-NPD	DDDII	HTLC	FDA-MDRegLC
BLC	PLC	TLC	TGA-MDRegLC
SG-CK-NPD	Bass	RE-AIM	HCanada-MDRegLC
CK-NPD	ILC	4S-IEE	HCTLC
	IC+		MDLS
	Norton-Bass		TPLC
	IEF		
	G-Bass-M		
	TALC-CAHF		
	TALC		

The broad perspectives are colour coded to highlight which stakeholder groups the types of lifecycle model/s originated from. The Hybrid models with an asterisk are those models that focus on outcomes evaluation in addition to either the NPD (usually) or diffusion process.

HC = green; Policy = yellow; T&I = orange; Reg = blue

6.1.1.4. Typology implications

Amongst fifty-two models, just eleven[i] were assigned to the outcomes evaluation archetype, with another four hybrid models that considered both outcomes evaluation and the NPD or diffusion process, all deriving from HC or policy. This suggests that outcomes evaluation is not a strong focus for the Reg and T&I perspectives. In fact, their main foci are on the NDP and diffusion processes. This is not surprising given that their goals are to improve the NPD and diffusion processes, but it does emphasise the fact that lifecycle evaluation does not always mean that it is the clinical outcomes associated with a product that are being evaluated.

These differences illustrate the fact that, despite using the same words, people can mean very different things. Consequently, there are very different motivations for using a lifecycle approach to evaluation. So, although the goal of healthcare is to improve health outcomes, requiring an outcomes evaluation focus, nevertheless, the literature shows

[i] One of these, the PrLC, evaluates end-user outcomes rather than patient outcomes, because it is not devised for health technologies, though it could potentially be applied to them.

that this is not what lifecycle evaluation is primarily about for other stakeholders – for many it is about controlling or improving diffusion or the NPD process.[286,154]

6.2. Thematic Analysis

I examined the models for the extent that they involved patients or end-users in the evaluation methods or processes contained in the models and found that this was minimal. Instead, the patterns in the data showed a strong pro-innovation and pro-adoption bias, as well as a desire for evidence to support decision-making and a need to apply controls to the processes involved. For all of these, the models played a role as communication tools for conveying their messages to their intended audiences. These themes are the subject of this section, each of which will be described briefly, with their potential impact on patients explored further in the discussion section.

6.2.1. Far from patient-centred

This theme was identified not by its prevalence across the models but, rather, by its lack. It might be assumed that patients would be central to any evaluation of medical devices, but amongst the models included in the synthesis there was a lack of patient involvement, either in the development of the model or in the evaluation process, with relatively few models examining patient or end-user outcomes. Only three of the included models involved[i] patients/end-users in the evaluation process with the primary aim of generating relevant evidence to improve their preferred outcomes.

A technology transfer model by Sheredos and Cupo involved identifying the needs of a particular group of patients (i.e. disabled US veterans), supporting the design, testing, commercialisation, and clinical assessment of technology to meet those needs, with clinical evaluation of the end-product, including user feedback.[244] Thus, end-users of these technologies were intimately involved in the evaluation process from start to finish.

Clarkson et al developed and proposed a model for conducting a '*systems-based user-centered*' medical device design and evaluation process that not only involves patients in the design of medical devices, but also in the design of the health system in conjunction with the device's design process in order to create a whole system that works for patients to meet their needs.[250] Commissioned by the United Kingdom's National Health Service (NHS), this model was developed in response to the need to attend more to patient safety. However, it is a high-level model that requires much additional work to operationalize and to implement, and it is unclear to what extent this model has been adopted within the NHS.

[i] By involved I mean that they weren't just the subjects of an evaluation of a procedure or device, but that they were actively involved or consulted regarding how an evaluation should be conducted and/or what was evaluated (in terms of outcomes that mattered to them).

These two models were unique in another way. Both were assigned to the Hybrid*[i] category rather than the Outcomes Evaluation category because they also focused on the development of the technologies. This means that in these two cases the evidence generation and outcomes evaluation of the technology is conducted by the developer from a healthcare (rather than an industry or profit) perspective, relieving the pressure to produce a monetary return on investment[ii], thereby, enabling a patient-centred focus. The third of these, the EUnetHTA-MDLC model, as shown in Figure 6.15, is comprised of three phases according to the types of activities performed during the life of a medical technology[iii],[291] but it is the two yellow boxes with the red outline that constitute their '*lifecycle approach to improve evidence generation*', which include Early Dialogues (ED) during the pre-market phase and post-launch evidence generation (PLEG) in the post-market phase.[292, p.22] EDs are requested from EUnetHTA by manufacturers to obtain scientific advice on the design of a planned study to be conducted prior to market entry. ED test pilot projects involved patients, with three different approaches being piloted for including patients' opinions regarding the evidence to be generated.[292, p.20-21] Patient involvement in pilot EDs led to changes in scientific advice regarding the desired clinical endpoint(s), adaptation of inclusion and exclusion criteria and the comparator[iv].[293] However, it is unclear whether this early scientific advice was followed by the ED applicant in their subsequent clinical investigation. The PLEGs have evaluated the use of patient registries as a means of generating evidence on safety and efficacy, however, though it was being planned, there appears to have been little patient engagement in this activity.[292, p.22]

None of the NPD models and few of the Hybrid or Diffusion models explicitly involve patients/end-users in determining how to evaluate outcomes from a product's use, although some NPD models do look for customer feedback as the final step in their product's development. Even amongst the Outcomes Evaluation models there was little involvement of patients, particularly in their development.

Most HC models made no mention of involving patients in the model development or in their outcomes evaluation process(es) even when their goal was to improve patient outcomes. One example, the IDEAL-D framework, involved gathering opinions from

[i] Although clinical outcomes from the developed device is their main objective, and these models were initially assigned to the outcomes evaluation group, their focus is as much on how to achieve good clinical outcomes through an effective needs-based development process as it is on evaluating the outcomes.

[ii] This is a significant pressure that those in industry face.

[iii] Rapid Relative Effectiveness Assessment (Rapid REA) generally occurs around the time of, or soon after, market entry, and full HTAs or REAs are conducted at a later stage when there is sufficient data to synthesise.

[iv] This included changes to include the relevant population subgroup(s), and a placebo comparator, which was found to be acceptable as a comparator for this particular patient group/clinical condition.

multiple perspectives. *'We undertook a modified Delphi survey to obtain expert opinion on how IDEAL might be used to evaluate medical devices and what modifications to the original version might be necessary. … The thirty-four individuals invited to participate in the survey included medical device industry and regulatory professionals, clinicians, research funders, researchers, methodologists, statisticians, and journal editors.'*[273, p.142] However, it appears that patients were not part of this development process, though industry was.

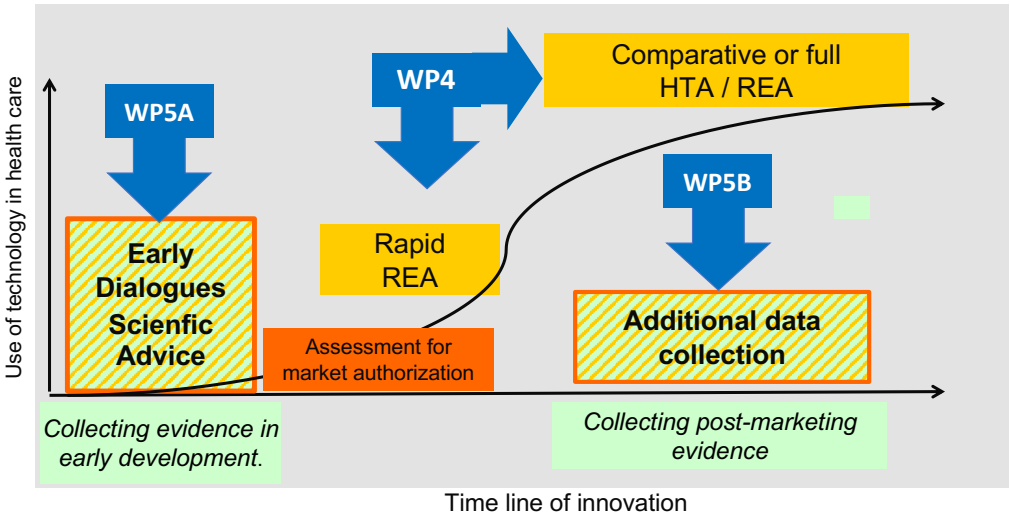

Figure 6.8. The EUnetHTA lifecycle approach to evidence generation.[291] (EUnetHTA-MDLC)[i]

Several HC models explicitly advised of the necessity of informed consent. *'Patients interested in innovative treatment should be adequately informed about all relevant aspects of the procedure and about the status of the treatment. This means that patients should be informed about the innovative character of the treatment …'*[270] However, if clinicians lack the information it is difficult to have an informed discussion with the patient. Patients/end-users were not involved in the development of any of the T&I or Reg models. Patients do not appear to be involved in the Reg evaluation process either, except for voluntary reporting of device-related harms.

There were some T&I models that did suggest involving patients/end-users in the evaluation process (e.g. SG-MDDP, Bhuiyan-NPD, SG-CK-NPD, TALC), but this was with the aim of improving commercial viability of the developed products. Having commercial success as the primary goal means that achieving the best outcomes for

[i] WP stands for Work Package. The EUnetHTA project that this was part of, EUnetHTA Project (2006-2008), consisted of eight work packages: https://www.eunethta.eu/eunethta-project-2006-2008/. WP4 worked on the common core HTA activities, whilst WP5 worked on how to adapt HTA to take contextual needs and requirements into account.

patients is a secondary goal. The focus on commercial success means that *'In order to create a new medical device, inventors and device companies must focus on the right clinical need. To that effect, a wide range of clinical needs are first identified through direct observation, by speaking with physicians, patients, and other health care providers, or through personal experiences, and by a review of the relevant clinical literature. Through a needs-finding funneling process (Fig. 10), inventors take a first pass at narrowing a large list of clinical needs based on the estimated market size and clinical impact associated with each. To further narrow the list down, inventors usually examine prior art related to each need to determine if there are barriers to further development from an intellectual property perspective*.'[154] This suggests, not surprisingly, that the 'needs' that T&I are seeking to address are primarily those that will produce a commercially successful product.

6.2.2. Pro-innovation bias – Why innovate – to improve health outcomes or profits?

A strong pro-innovation focus was found across most of the models included in the synthesis. As can be seen from Figure 6.15, approximately two thirds of the models focused on evaluating innovative products or technologies rather than evaluating established technologies or all vintages of device[i].

This pro-innovation tendency was also acknowledged by model authors. Rogers considered this to be one of the limitations of diffusion research,[123, p.104-135] whilst Greenhalgh et al echo his sentiments, '*However, the early tradition had a number of theoretical limitations,… These include pro-innovation bias (the notion that anything new is better than what has gone before and that adoption is more worthy of study than non-adoption or rejection), individual blame bias (the stereotypical and value laden terminology for describing adopters, such as 'early adopter', 'laggard'), a tendency to assign causality when such a link was not justified, and the implication that the findings of diffusion research were independent of context and setting*.'[294, p.10]

[i] That is not to say that the models cannot be used for established devices or for devices of all vintages, only that the focus is on primarily on new devices. Of course, a lifecycle approach means that these new devices will grow old and, presumably, established, but the models are particularly interested in evaluating newer devices and significantly less interested in older ones.

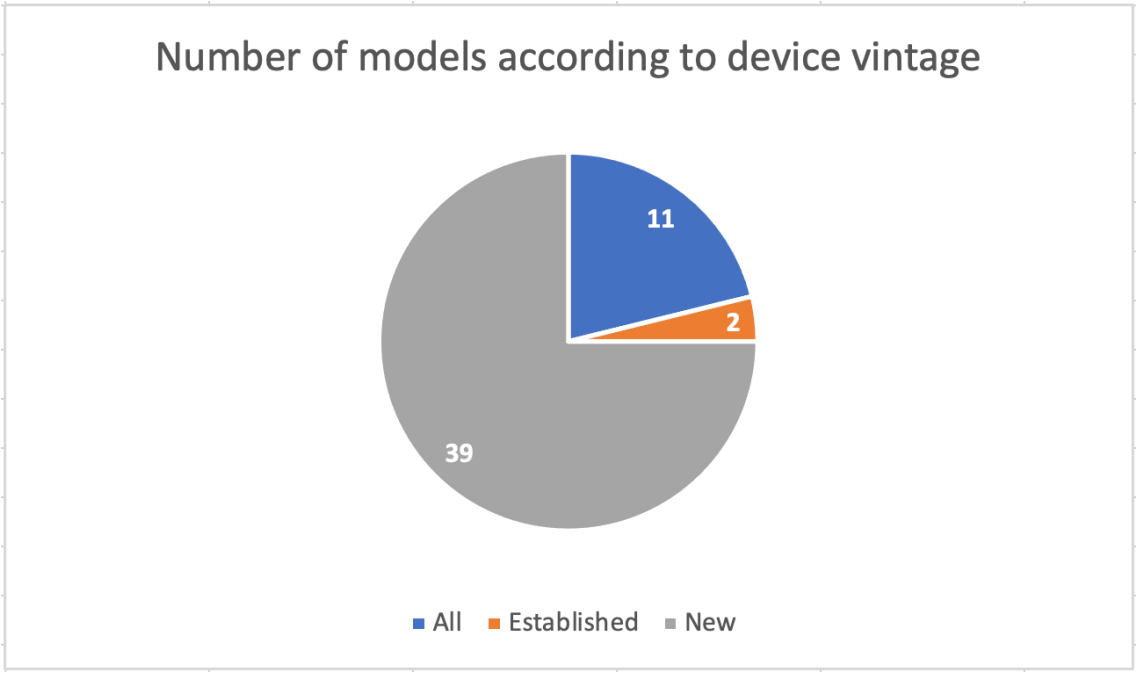

Figure 6.9. Summary of models according to their focus on device vintage

Furthermore, the pressure to innovate is pervasive. Innovation is considered to be an imperative for success, both commercially and as a means of improving health care.

'Why Invest in Innovation? It can lead to higher profits. Firms with innovation as a primary strategy realize 29% higher return on sales compared to those with other primary strategies (Georgia Manufacturing Survey 2012).'[295, p.1]

'With product lifecycles that are sometimes as short as 18 months, patients benefit from a continuous stream of innovation that hinges heavily on successful needs assessment and the experience and skills of engineers and other professionals involved in the innovation process.'[154, p.021004-1]

However, not all innovation produces a novel product. Croslin refers to first-in-kind innovations as invention,[260] thereafter incremental innovation to the original product may enhance functionality and profits. Indeed, the effect of introducing multiple generations of a product on sales, and consequently profits, is illustrated by Norton and Bass's model (Figure 6.10),[235] which demonstrates that the level of sales grows exponentially with each new generation, each of which is essentially an incremental innovation improving upon the original 'first-in-class' product. This anticipated increase in sales from subsequent generations is clearly an incentive for industry to innovate incrementally.

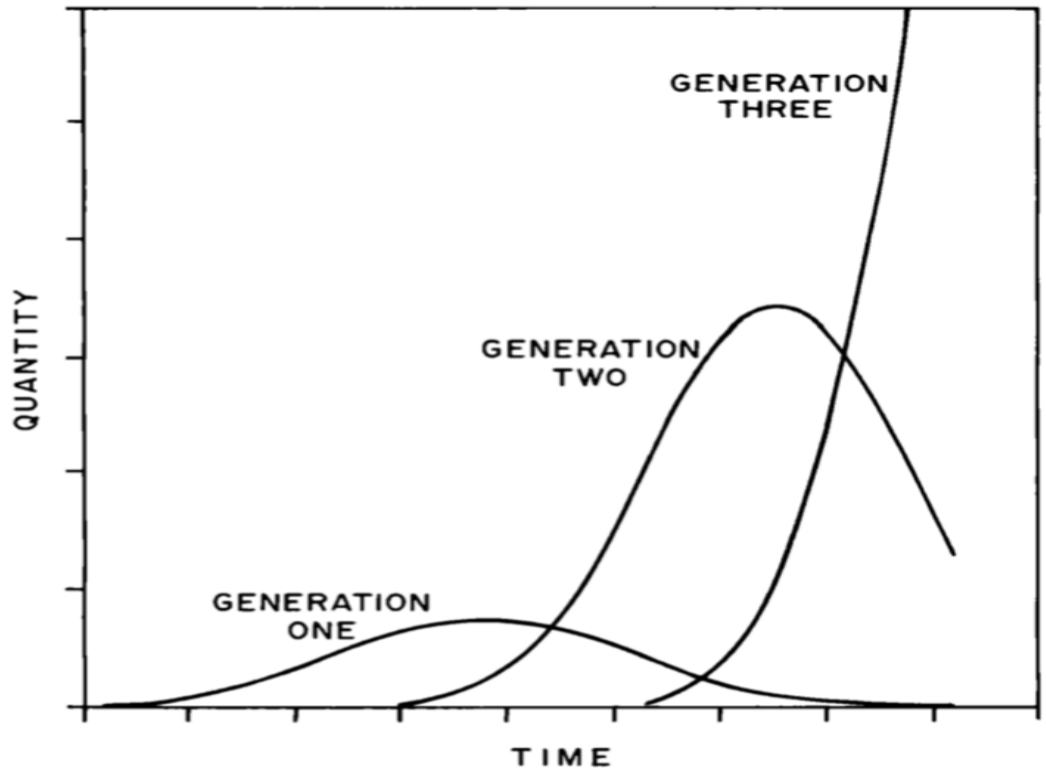

FIGURE 1. A Series of Technological Generations.

Figure 6.10. Figure extracted from Norton and Bass illustrating the exponential increase in sales observed for subsequent generations of a product.[235]

However, Croslin also points out that continued incremental innovation will likely reach a point where the innovations are negative, reducing the value that consumers gain from the newest version.[260] In the case of implantable medical devices the clinical cost of this can be significant, as Hannan et al explained: *'A 2011 analysis of the AOANJRR showed that no hip or knee arthroplasty introduced in Australia between 2003 and 2007 had improved outcomes over those currently being used. Of those introduced, 30% were associated with significantly worse outcomes.'*[11, 276, p.1] In fact, the authors of that study concluded that '*It could be argued that if no new hip or knee prostheses had been approved for use during the study period, then the overall outcome for both hip and knee replacement surgery may have been better.*'[296, p.53]

Across all the models there was a clear sense of the near universal belief in innovation and of its necessity for improving healthcare (even within the HC models designed to restrain the diffusion of unevaluated innovations) as illustrated by the selection of quotes in Box 6.1.

Healthcare models – authors explicitly or implicitly demonstrating faith in the principle of innovating for improved healthcare
'Innovation should be encouraged; however, clearly defined and nationally recognized strategies should exist to bring new implants into the public/patient domain with patient safety and protection being the major prerequisite.'[276, p.1]
'*Innovation is required to develop novel interventions in order to improve quality of care. While surgeons are highly innovative, the uncontrolled introduction of unproven innovations may have adverse consequences for patients. The purpose of this article is to propose an innovation cycle whereby surgical innovations can be safely introduced into clinical practice, …*'[267, p.e164(1)]
'*For the patient, the most important criteria of an innovation are safety, efficacy, and effectiveness. Hovering over this goal is the underlying principle to support the freedom of science and the freedom of physicians to develop the best possible procedure in order to reach the best obtainable outcome for their patients, …*'[261, p.1595]
'*We have focused on the intricate relation between innovation and practice in surgery, and how this needs a formalised evaluative framework.*'[256, p.374]
'*Invasive medical devices have transformed the way modern medicine is practiced. Devices such as pacemakers, intravascular stents, and artificial joints provide new options and make treatment possible for previously unfit patients. Unfortunately, several high profile medical devices have resulted in significant patient harm [1,2].*'[111, p.141]
'*Clarifying the boundaries between research and treatment and identifying the distinctions and gradations between them can benefit patients both directly (by way of safeguarding the possibility of offering chances as well as minimizing the exposure to risks and negative effects) and indirectly (through the advancement of medicine and the contribution of data to a growing body of knowledge).*'[270, p.417]
'*For persons with disabilities, the proliferation of technology has helped to enhance their performance of life and work functions. They have used it to overcome barriers and become active, participating members of society. A large part of successful technology application relies primarily on effective mechanisms that help bring emerging research and development (R and D) prototypes from the lab into the commercial marketplace. … The ultimate goal is for timely transition of prototype developments into commercially' viable products and techniques that can be readily available and accessible to benefit veteran and non-veterans with disabilities (Fig. 1).*'[244, p.25-26]

Box 6.1. Quotes from HC models illustrating their focus on innovation

Thus, two key assumptions underlying this pro-innovation bias are that innovation means new, and new means better, but as it has been shown, neither of these is always true, often they are false. Without assessing the evidence (or when there is no evidence) it remains unknown whether an innovation is better or worse than what went before.

6.2.3. A pro-adoption bias

A propensity to favour adoption, particularly of innovations, was a common theme, as evidenced by the fact that the primary focus of attention was on diffusion for seventeen of the fifty-two included models, making this the commonest of the three model archetypes. Many of the Hybrid models also featured approaches for facilitating adoption as previously described in the model typology section. The Outcomes Evaluation models

all propose methods of evaluating health technologies, many of which are based on the premise that the innovation will be adopted, with or without evidence of its effectiveness/safety. In fact, even the NPD models included diffusion considerations as part of the NPD process in all but three (MDDP, Bhuiyan-NPD, IRM-SaMDDP).

Furthermore, despite many models proposing methods to limit diffusion, this pro-adoption stance was evident across all perspectives. It is not surprising that the T&I models would favour adoption, but it is somewhat surprising that adoption or, its counterpart, diffusion has a more predominant place than the evaluation of clinical outcomes for most of the models arising from the Policy and Reg domains.

However, innovation and adoption are closely linked, as innovation can only yield its benefits, whether to industry or to patients, through its adoption, and, since innovation is universally considered to be intrinsically valuable, adoption is, therefore, expected and assumed to be the appropriate choice, given the tacit assumption that new is better.

Within policymaking this is evidenced by a continuing focus to promote innovation adoption. *'How the new Procurement Directive may contribute to spur innovative purchases in the health sector.' … 'STRATEGIC use of pp [public procurement] to stimulate innovation, ….'*[297, notes section slide 1](Capitals in original)

This is the case even when there is an acknowledgement that the pro-adoption stance may not always be the most appropriate focus[i] - '*This article summarizes an extensive literature review addressing the question, How can we spread and sustain innovations in health service delivery and organisation?*[251, p.581] This particular model, the DDDII, was later expanded, or became the springboard for another Policy model that focussed instead on non-adoption, the NASSS framework, with the intention of gaining an understanding regarding why promising technologies are not adopted. So arguably, the focus remains on adoption (even if this is from the other end of the adoption spectrum), and certainly neither of these models are focussed on outcomes evaluation, they are diffusion models.

Indeed, only one Policy model author created a lifecycle model with the aim of dismissing it.[76]The model described by McKinlay is the pattern that he has observed over the life of new health technologies, but not one that he recommends.[76] Using the diffusion model he describes, he highlights how little evidence is available for medical innovations when they are introduced, adopted by physicians, and later accepted as normal practice by the public and healthcare payers. He argues that this is bad for patients, payers, and healthcare. His model is intended to make us aware of the unacceptable level of

[i] '*These include pro-innovation bias (the notion that anything new is better than what has gone before and that adoption is more worthy of study than non-adoption or rejection)'*.[294, p.10]

evidence available for medical innovations. He then proposes an alternative – the assessment of population health needs and a thorough assessment of innovations regarding their safety, effectiveness, cost-efficiency, appropriateness, and equity of access prior to allowing them to be publicly funded.[76] He effectively dismisses the lifecycle approach and instead calls for a comprehensive assessment of an innovation before allowing its publicly-funded adoption. This contrasts with all the other models, which are described so that they can be used (not dismissed) to guide strategic planning or specific activities. He is in effect calling for the conduct of HTA on all new health technologies[i] before they are allowed to be adopted by healthcare services.[76] However, HTA is a research discipline that mostly evaluates existing evidence[ii], it cannot evaluate evidence that is not there, and there is generally a lack of data for evaluating medical devices. Indeed, it is this lack of data that is driving HTA to seek lifecycle approaches to evidence generation and evaluation. '*However, having in mind its definition and privileged position, HTA activities have evolved to more constructive approaches from health technology inception to its obsolescence (Henshall et al., 2011). New concepts such as scientific advice (Jost et al., 2015), early dialogue, early awareness, and alert systems (Packer et al., 2012), post-introduction observation of health technologies (Varela-Lema et al., 2012), appropriateness, re-assessment, and disinvestment (Elshaug et al., 2007) have gained ground.*'[275, p.1]

Nevertheless, HTA is also put under pressure, even from healthcare, to advise in favour of adoption, and perhaps to not expect to have the necessary or best evidence for decision-making. *'Therefore HTA bodies need to balance the demands of regulators to decide on the best available evidence in relation to the innovation with the patient's right of access to the best and most useful procedure to reach the desired outcome.'*[261, p.1607]

In this case, and in healthcare generally, adoption is often equated with patient access, and it was clear from the models that there is an implicit belief in the importance of early patient access, and subsequently, inherent pressure to ensure patient access to innovation, even whilst attempting to ensure that there is sufficient evidence before allowing adoption. '*The innovation cycle, if followed correctly, could ultimately save money and provide better outcomes for patients*.'[267, p.e164(5)] However, as Hannan et al and many other HC model authors argue, early access without evidence is unlikely to be in the patient's interest. '*Forsaking new technology completely to avoid all possible risks to the public will reduce the quality of health care in the long run. There needs to be a*

[i] Whilst he focusses on 'career' of an innovation, McKinlay also advocates for the evaluation of established technologies that have little evidence supporting their use.

[ii] Although individual HTA bodies have been known to conduct primary research to generate the missing evidence, but this is relatively infrequent. Examples include research by Poder on smart pumps [298]; Kelly et al on antimicrobial wound dressings [299]; and Pedersen et al on Chronic Fatigue Syndrome.[300]

middle ground found where new implants can be evaluated and introduced in a safe and regulated manner.' [276, p.4]

This is particularly true if this early access is not in the context of a clinical trial, which at least would help to ascertain what effects are due to the device, and which are not related to the device itself, to better inform future healthcare decision-making.

6.2.4. A need for control and a need for evidence

An overarching theme is the need to acquire more information or evidence to inform decision-making. In fact, all the models address an information need, and are used for gathering, generating, or conveying information/evidence required for making the best decisions to achieve the overarching goal. However, the decision being made and, therefore, the type of information or evidence required to inform it, varies significantly across the different perspectives. This theme has largely been covered in the Goals and Purposes section of the Comparative Analysis under Goals and Purposes.

However, I return to it here because there remains a lack of evidence for most medical devices on the market, and it is because of this that a lifecycle approach to evaluation is proposed.[61] Indeed, for most devices the evidence generally remains poor. Figure 6.18 attempts to combine several of the models into one, to illustrate the limited nature and type of data that is generated and the types of data made available across the lifetime of multiple generations of a device. The Norton-Bass model informed the shape of the curves regarding the numbers of products being sold/used across multiple generations of a product,[235] whilst the type of evidence available is taken from McKinlays' model,[76] with the types of data generated being gleaned from WHO's MDLS model and from regulatory guidance documents.[97] It shows the chronology whereby each lifecycle evaluation model archetypes is predominantly being used for a given generation of the device, with the NPD models naturally being used predominantly at the development stage of each generation and the Diffusion models being applied more particularly at the earliest stages in its diffusion, but it also shows that the Outcomes Evaluation models are mostly only applied later in the life of a particular generation of the product. The diagram illustrates the fact that at the earliest stages of the first-in-class device there is

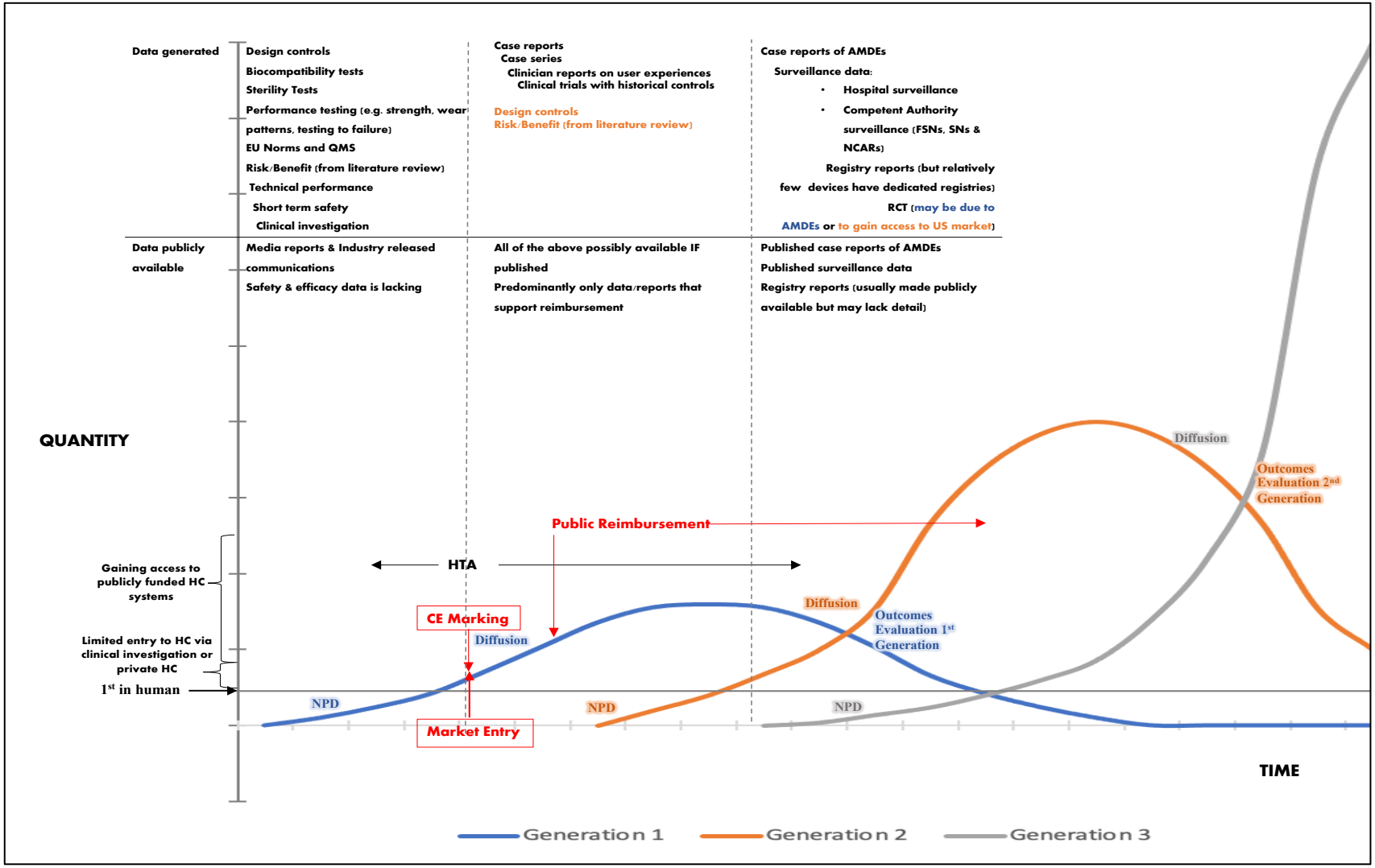

Figure 6.11. The multi-generational lifecycle of a device illustrating the typical evidence available over the lifecycle.

very little data generated and even less available, but whilst additional data is generated over time, very little of this is made available, and then usually only if it is published. Furthermore, the earliest types of data generated include pre-clinical tests, and data related to compliance with standards and quality systems, none of which is publicly available. Later, case reports appear, if they are published, otherwise media reports and advertisements making marketing claims constitute the available 'data'.[76]

The x-axis illustrates that devices gain market entry with little clinical data, whilst pressure is applied to conduct HTAs as early as possible for first-in-kind devices; and if the device shows sufficient promise, it may secure public procurement. Once in the healthcare system there may be reports published on its use, or incidents and AMDEs reported to surveillance authorities. However, before the original device's use goes into complete decline, a new, 'improved' version is launched, gaining entry to markets on the basis of substantial equivalence, and entering the healthcare system using the same funding pathway, by competing with its parent/first generation product. According to the Norton-Bass model, its uptake overtakes that of the original device,[235] yet it has little, if any, clinical data of its own.[86] As it is used by more clinicians or patients, further adaptations are made to create a more sophisticated version, an upgrade to the second generation.[154,224] The upgrade again gains market entry on the basis of substantial equivalence and entry to reimbursement funds in the healthcare system on the basis of being a competitive alternative to a device that is already being funded.[301,272] Furthermore, much of the clinical evidence used to gain market entry is based on observational data, with very few devices undergoing clinical trials, whilst the quality of the trials is frequently poor for those that do undergo a trial.[75,86,302–307]

Another recurring theme across all models is the issue of control, with many models describing ways and means of influencing or controlling medical device lifecycle processes (or their outputs), mainly the NPD or diffusion processes, but also seeking to influence device use and evaluation methods. The control theme is presented here in combination with the evidence theme as they are interrelated because some models seek to impose controls until more evidence can be generated or becomes available, whilst others seek evidence to influence or impose control over a specific key process (such as the NPD or diffusion activities). For the most part, HC models seek to control diffusion, to limit it, until evidence has been generated for optimal clinical decision-making. This is also true for some of the Policy models. Most of the T&I models are focused on gathering or describing the evidence needed to control the NPD process, or influence their products' diffusion, which is also true for some of the Policy models. Some of the T&I models refer to these internal NPD controls as stage-gates, which are only opened to allow innovations that meet certain criteria to pass through to the next stage

of development (CK-NPD, SG-CK-NPD, Bhuiyan-NPD, SG-MDDP). Three of the Policy models refer to these gates as 'technology readiness levels', which are used to guide decisions regarding whether a technology is sufficiently developed to allow it to move to the next level of development and use (TRL, IRM-TRL, PrLC).

Most of the Reg models describe the regulatory activities and regulatory controls in terms of the requirements placed on devices and/or the relevant processes for producing and selling them, to ensure that devices entering the market meet the regulatory requirements. *'The current regulatory system of product market authorization is one where the terms and conditions of market authorization (licensing) are based on the knowledge and assessment of a product's benefit-risk prior to marketing, such as safety and effectiveness information*[i] *obtained from clinical trials*.'[265, p.7]

Pre-market control is performed on the device to ensure that the ***product*** *to be placed on-market complies with regulatory requirements. Labelling and advertising control is maintained for correct* ***product representation****. Placing-on-market control ensures establishment registration, device listing and after-sale obligations. Post-market surveillance/vigilance ensures the continued safety and performance of devices in* ***use***[ii]*.*[97, p.10]

Reg models impose controls and demand evidence for the pivotal market entry decision, which they control. The HC and T&I models focus on applying controls on themselves (i.e. insiders advising peers), whilst Policy and Reg models are intended to exercise control or influence on the actors involved with medical devices (i.e. they are outsiders imposing controls).

However, the main difference between the regulatory and some of the other models, particularly the HC models, is in the degree of power that they have to impose the controls described in their models. Healthcare actors have very little control over the diffusion of health technologies, and what control they do have lies in being able to refuse to buy devices until the evidence is made available. Once health technologies are funded

[i] It is worth noting that *'<u>such as</u> safety and effectiveness information'* is not the same as saying that safety and effectiveness information obtained from clinical trials is required for authorisation or that all device authorisations are based on this. Although it gives the impression that this is the case, it doesn't mean this. What it means is that some devices are authorised on the basis of this clinical trial information, but not all.

[ii] Note that the pre-market requirement is that products comply with the regulatory requirements and that Cheng doesn't make any claim for their being evaluated for their safety and effectiveness in the pre-market phase. Whilst in the post-market phase he writes that surveillance '*ensures the continued safety and performance'*, which means, firstly, that he also makes no claim for their effectiveness in the post-market phase, and secondly, he implies that the safety of devices had already been evaluated and passed in the pre-market phase.

and have entered the healthcare system there are very few mechanisms available to impose any controls on their diffusion, uptake, and use.

Nevertheless, even the regulators' power to impose controls is somewhat illusory, because if they are not given the resources to do their job they cannot enforce their control mechanisms, and this is particularly true in the post-market phase. In the pre-market phase manufacturers and vendors are compelled to comply in order to gain admittance to the market, therefore, the incentives for compliance are very high. Whereas in the post-market phase there are few incentives for compliance, having already gained market entry, further compliance is a cost with limited return.

6.2.5. Models as a communication tool

An important aspect of all the models is that they are intended as a means of communicating a message to a particular audience. Models serve not only as tools for evaluation but also as an heuristic for describing, explaining, predicting, presenting, or prescribing behaviour in a concise manner that involves communicating meaning.

Rogers describes two types of communication involved in the adoption decision process – communication to impart knowledge (i.e. making people aware or teaching the skills needed to use the innovation) and communication to persuade (by this he means to form an attitude towards the innovation, whether to adopt or to reject).[137] These two types of communication are also evident in the NPD, Outcomes Evaluation, and Hybrid models.

As has been shown from the previous descriptions, for most of the models the main ideas that are communicated are 'how to'. How to develop new products, limit or promote adoption, increase sales, evaluate outcomes, and regulate devices.

The models convey ideas suggesting the best ways, or the best processes to follow, to achieve the goal of each. Such models are intended to increase knowledge.

For example, Pietzsch et al in their model suggest an evidence-based approach for improving the development of new medical devices. *'This paper reviews existing model representations and presents a new comprehensive development model that captures all aspects of device development and commercialization from early-concept selection to postmarket surveillance. This model was constructed based on best-practice analysis and in-depth interviews with more than 80 seasoned experts actively involved in the development, commercialization, and regulation of medical devices.'*[154, p.021004-1] Moore

considers his to be the best marketing approach[i]. '*But I do claim that they are the best I know of, and that they are representative of best practices …*'[238, p.154]

However, whilst most models aim to increase knowledge, frequently a key feature of many of them is the intention to influence the opinions and attitudes of their target audiences through the medium of the model and the message(s) it contains. Many of these messages are self-evident and the target audience is clear.

For example, the HC models seek to persuade surgeons of the necessity to limit the adoption of untested innovations until they are evaluated, and to adopt the stage-specific study designs that they propose with the aim of improving the evidence base. *'The IDEAL model is based on the suggestion that surgical innovation and evaluation can and should evolve together in an ordered manner from concept, through exploration, to validation by randomised trials (panel 1)*[ii] *.'*[110, p.1109]

Certain Policy models seek to persuade policymakers to adopt methods facilitating uptake of new health technologies. *'Other authors (whose work is summarized in the Results section below) have drawn on such literature to produce unifying frameworks aimed at informing the work of implementation, although no previous framework has focused explicitly on nonadoption, abandonment, scale-up, spread, or sustainability.'* [274, p.2]

Authors of the T&I models seek to persuade those from trade and industry to adopt ways of improving their NPD or diffusion (i.e. sales or marketing) processes. For example, Levitt suggests that '*Now that so many people know and in some fashion understand the product life cycle, it seems time to put it to work. The object of this article is to suggest some ways of using the concept effectively and of turning the knowledge of its existence into a managerial instrument of competitive power.*'[224, p.81]

These forms of communication are obvious in their intent. What is not so obvious is the intent behind some of the Reg models - that the regulators are trying to persuade the general public of their effectiveness. Nor is it so obvious that they are seeking to justify their approach to regulating medical devices.

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[i] He argues that the best way to market high-tech products is to create a relationship with your customers; understand what it is about them and the product that 'compels' them to buy; create a 'whole product' approach by developing alliances with complementary product producers; identify and target the marketing niche that your product is most likely to be able to fully occupy; develop the competitive strategy needed to 'win' that market, by making it easy for consumers to buy the product; select the appropriate distribution channels for gaining access to the mainstream market and a pricing strategy designed to encourage the distributors to favour selling your product over competitors.[238]

[ii] Though it also suggests that it might not always be possible for a procedure to evolve in an '*ordered manne*r', '*This order does not always reflect real situations, in which the timing and nature of evaluation might depend on the type of development*.'[110, p.1109] However, they do want their audience to adopt their proposed approach and the stage-specific study designs that they propose.

For example, the following quotation suggests that medical devices have been evaluated thoroughly in the pre-market phase before allowing them onto the market, but at the same time persuading their audience, the general public, that device safety relies on vigilance so as to encourage reporting of adverse outcomes. *'Because of the increasing number and complexity of products used by Canadians to maintain and improve their health, it is important that Health Canada's product vigilance system remain open, transparent, accessible and accountable. Products available for sale in Canada have undergone a rigorous assessment and meet high standards of safety, quality and efficacy. The continued safe and effective use of these products depends on a thorough and ongoing understanding of the benefit-risk as they become known through real-world experience.'*[265, p.1] This quotation is extracted from the Health Canada guide to vigilance, but it could have come from any of the regulatory models, because it is the message that all regulators wish to communicate to the public.

Even Swissmedic, which is more explicitly clear that devices are not authorised[i] for market entry, frames its message in language that implies that the regulatory approach is valid and acceptable when it states that '*Compliance with internationally valid norms is evaluated by private entities.*'[278] What is not explained is that these 'norms' are standards that are not publicly available for scrutiny and that industry representatives were/are intimately involved in their development. Nor is it clearly stated that their validity rests on vested expert opinion rather than on any validation process.

In fact, I would argue that the lifecycle concept has been used to justify how regulators regulate medical devices.[301] For example, the Total Product Life Cycle (TPLC) model was first presented by the US Food and Drugs Administration (FDA) as a way of justifying its new regulatory approach to medical devices following the introduction of legislation in the Senate that limited their ability and funds to evaluate medical devices.[301,308,309] The burgeoning number of medical technologies and the overstretched resources of the FDA meant that they were not in a position to evaluate the safety and effectiveness of all devices seeking entry to the US market.[308,309] Consequently, they adopted a risk-based approach, only evaluating those devices that they deemed to be high-risk in the pre-market phase using their most rigorous evaluation process, which examines the safety and efficacy/effectiveness of the device, whilst medium-risk devices could be allowed to enter the market on the basis of being substantially equivalent to another legally marketed device, known as a predicate, and were/are considered safe and effective on the basis of equivalence.[57,309,310] This is explained in more detail in Box 6.2.

[i] Authorisation suggests that the regulators have evaluated and approved them as safe and effective.

Background to the FDA's TPLC model

One of the first medical device regulators to explicitly adopt a lifecycle approach to regulation was the FDA with its TPLC. They were under increasing pressure as the numbers of new technologies that required assessment was growing dramatically, their budget was not increasing in line with the increased demand, and Congress was demanding that they take the '*least burdensome approach*' for industry, enforcing it as a legal requirement.[301, slide 14] '*Historically FDA's role has focused on the consumer protection provided during the premarket evaluation of new products. Even congressional budgeting language will often earmark this phase of drug and device development. In the FY 2000 budget the appropriation specified a floor of effort of slightly more than half of the Center's budget and FTE's for the premarket program. Logically then we are able to divide a product life around the pivotal marketing decision and can describe a product life cycle as a two cycle: pre and post.*' [301, slide 7] The TPLC was the result of this.

Philip Phillips[i] reported to the workshop convened by the Institute of Medicine (IOM) that '*The PMA process was so burdensome and demanding that there was pressure in the agency to bolster the concept of substantial equivalence, which would allow products to go to market quickly with appropriate safeguards. Substantial equivalence evolved to compensate for regulatory realities.*'[311, p.9] He also reported that '*Although Section 510(k) was initially intended to be the principal means by which new medical devices were classified, the 510(k) program has evolved in an effort to meet the challenges of a diverse and rapidly changing industry and a highly scrutinized regulatory agency that has never been provided with the necessary resources to meet everyone's expectations.*' [311, p.75]

This approach involved dividing devices into groups based on the perceived level of risk that they posed and requiring direct clinical evidence only for the highest-risk devices (i.e. clinical evidence on the device itself and not on a similar device), which was then evaluated by the FDA. Taking this approach meant that the regulator was generally not required to evaluate the lowest-risk devices and they could be placed on the market without evidence presented of their efficacy. For medium-risk devices, it was required only that the manufacturer or relevant economic operator demonstrate equivalence with a device (predicate) that was already legally marketed. This is known as the 510(k) regulatory pathway, and for this the FDA need only evaluate whether the device is substantially equivalent to the predicate. Based on its equivalence it was then presumed to be safe and effective, and was allowed to be placed on the market, subject to certain controls[ii].[312] '*Also known as premarket notification, the process in Section 510(k) of the Federal Food, Drug, and Cosmetic Act requires a manufacturer of medical devices to notify FDA of its intent to market a medical device at least 90 days in advance. That window of time allows FDA to evaluate whether the device is substantially equivalent to a product already on the market, in which case the device does not need to go through the premarket approval process.*'[311, p.1]

This reduced the pre-market assessment work that the FDA had to complete, and allowed it to rely on PMS to detect devices with safety issues. However, as direct evidence was not required to gain market entry, it also resulted in less evidence being generated and/or made available. Thus, one of the main reasons for the lack of clinical evidence available at market entry of a 'new' device is the adoption of a lifecycle approach to regulation. Not only has it resulted in less evidence being available, but the evidence that is available is of poorer quality, since most of the post-market evidence is observational rather than clinical trial evidence.

Box 6.2. Additional background to the history of the FDA's adoption of a lifecycle approach - the TPLC

[i] Phillips was an independent consultant at the time, but had 24 years of experience working in the FDA and had at various stages acted as the director of program operations, interim director for the Division of General and Restorative Devices, deputy director for science and regulatory policy at the Office of Device Evaluation, deputy director for the Division of Ophthalmic Devices, and chief of the Diagnostic and Surgical Devices Branch. [311, p.73]

[ii] Such as good manufacturing practice, registration, record keeping, application of standards, labelling requirements, device-specific testing, and reporting AMDEs to the FDA. [Internet]. Accessed 2018 Feb 06. Available from: https://www.fda.gov/ForPatients/Approvals/Devices/ucm405428.htm

Other jurisdictions also use a risk-based approach to regulation, including Australia, Canada, Switzerland, and the EU, which is reflected in the models. Indeed, WHO recommends taking a risk assessment approach to regulation: *The Guide begins by explaining how safety is a risk management issue, and how optimum safety and performance require cooperation among all who are involved in the life span of a medical device.*'[97] This reframing of safety to be a risk management issue conceals the fact that safety is not evaluated, risk is. Nevertheless, no matter how important risk management is for containing risks, it tells us little about actual outcomes. Furthermore, device performance is not the same as clinical efficacy. A device may perform well yet not provide the clinical outcomes expected or hoped for by patients. '*For example, radiofrequency ablation devices, used to destroy liver tumours, were approved for use after the sole demonstration that they could destroy liver and tumour tissue.*[41] *Indeed, there was no requirement to show that, by doing so, this technique was as effective in terms of cure as the pre-existing standard of practice—ie, surgical resection*.'[256, p.1091] Similarly, the morcellator, a device that is used to shred tissue into smaller pieces to remove them through small openings, was approved via the 510(k) pathway and was deemed to be effective at removing uterine fibroids laparoscopically, despite the potential risk of causing widespread dissemination of malignant cells around the body, which is what happened for a number of women.[313,314]

6.3. Discussion

The differences noted in Tables 6.4-6.5 illustrate that, despite using the same words, people often mean very different things and have different reasons for using a lifecycle evaluation approach. Furthermore, there are a number of assumptions underlying the models, the themes described, and the use of a lifecycle approach that are relevant to patient safety, some of which I have already explained, but there are others, which I will now expand on.

6.3.1. Assumptions affecting patient safety

It is the lack of evidence available for decision-making at market entry and when reimbursement is being sought that is driving the push to adopt a lifecycle approach to evaluation for healthcare reimbursement decisions.[243] Indeed, there is a tacit understanding that a lifecycle approach to evaluation is necessary so that beneficial new technologies can enter the market earlier despite insufficient evidence, and that this lack of data is acceptable if we take a lifecycle approach. It is assumed that this will identify any devices that are unsafe and provide additional evidence of clinical benefit. Further

assumptions are that innovative devices are more likely to be beneficial than not and that more data will become available over time. However, the validity of these assumptions has not been subjected to sufficient scrutiny despite significant evidence to the contrary.[30,256]

Furthermore, the lack of evidence available at market entry/reimbursement is related to the adoption of a lifecycle approach by medical device regulators. As Herder explains, *'The concept of lifecycle regulation … also refers to an approach to regulation that factors the prospect of evidence generation postapproval into preapproval decision making'*.[309, p.824] Therefore, adopting this approach has meant that they have accepted limited and poor quality evidence, allowing devices to enter the market based on the expectation that more evidence will become available once the device is in use.[309] Yet, this is frequently not the case.[304,315,316]

Once on the market the regulators rely on post-market studies to address uncertainty regarding effectiveness, and they rely on vigilance and surveillance activities to detect adverse outcomes. However, Rathi et al have shown that many post-market studies are slow to be completed or not conducted at all, meaning that additional evidence on effectiveness does not become available for many years, if at all.[86] Post-market surveillance is designed to detect only the most severe adverse outcomes,[317, p.6-7] which are just the tip of the iceberg of all the adverse outcomes that affect patients.[25] Furthermore, clinicians and patients are not readily made aware of the evidence regarding a device's poor safety record, as demonstrated by Peters, Pellerin, and Janney, whose study showed that recalls of Class III devices in the US took up to 259 days from initiation to completion, Class II took longer, and Class I devices took more than twice as long.[11]

Additionally, several authors have demonstrated that though a device has been recalled it may still be used as a predicate (i.e. a substantially similar device legally placed on the market) to support the market authorization of many subsequent devices through equivalence claims.[302,310,318–320] This means that not only is there a lack of evidence regarding the safety and efficacy of the particular device, but the evidence from the predicate device upon which its approval is based suggests that it is likely to be unsafe. Thus, the bar for the evidence of safety and efficacy needed to support a device to gain market entry is low, whilst the bar for accepting evidence against a device, even regards its safety, is high. White and Walters refer to this as a permissive regulatory approach to market entry arguing that it is '*based in neoliberal tenets, where risk, in the form of adverse events, is inherently tolerated within governance structures, evidencing risk*

colonisation'[i],[321, p.358] They argue that it is ethically necessary to apply the precautionary principle to assessing benefits and risks of medical devices, because it is '*not possible given the 510(k)'s basis in analogy decision-making*,'[321, p.374] for clinicians to explain the risks of the device to patients, making informed consent impossible.[321]

The assumption that innovation is good and improves health outcomes also implies that early access is essential for patients to avail of this presumed benefit as soon as possible. In fact, governments may be put under pressure from patient advocacy groups to provide rapid access to innovation, and they are certainly put under pressure to provide pathways for introducing 'innovative' products into healthcare.[272,286]

Early access also means selling products sooner and selling more of them before competitors begin to enter that market, thereby allowing innovators to recoup their development costs and gain competitive advantage. However, early access usually means that products are approved for funding and enter public healthcare systems with little data and limited evidence regarding their safety and effectiveness as measured by meaningful patient outcomes in relevant patient populations.[30,322]

This is a major concern since allowing early access without data means that manufacturers don't need to provide much evidence to secure reimbursement, and additional data is frequently not collected or made available in a timely manner, unless funders require it or safety issues prompt concerns.[256] In fact, it has been shown that earlier access to newer devices with less data, and without pre-market assessment of clinical effectiveness, results in more device failures and more patient harms.[323] This means that providing earlier access, with less data, for increasing numbers of new devices simply puts more patients at risk without guaranteeing either their clinical effectiveness or the generation of the appropriate evidence necessary for the assessment of their clinical effectiveness and safety.[76] Further, it is often harder to remove a product from a country's list of provided therapies than it is to introduce it, even if evidence later becomes available that shows inferior efficacy.[309]

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[i] They explain risk colonisation by drawing on Rothstein, and argue that '*The laxity of this analogy-based decision-making approach evidences the risk colonisation theory Rothstein (2006) discusses, where governance failures in managing risk are assumed, and bureaucratic structures justify risk trade-offs. As Rothstein (2006) scrutinises, this dynamic draws the attention of regulatory organisations away from societal risks, and instead focuses them on reputational risks of the organisations themselves. The 510(k) process offers a veneer of risk assessment, but one that lacks meaning when pre-1976 products are the basis of risk assessment and products used for hernia, cardiac, and rotator cuff repair may serve as the basis for products used in urogynecology without prior sex-specific testing. Ultimately, it seems that the concept of 'innovation' has usurped this risk assessment process*.'[321, p.372]

Furthermore, most post-market data is observational in nature, which cannot assure us of a device's efficacy. Observational data has value, but not for answering questions of efficacy or comparative effectiveness. However, the main problem with observational data, often referred to as 'real world data' (RWD) or 'real world evidence' (RWE), and its generation is that it means that a device must be used on patients before there is evidence to support its use, and whilst this may be acceptable within the context of an RCT where the uncertainty of effects is being tested, the generation of RWD does not usually occur in the context of a clinical trial, which again means that it cannot provide reliable estimates of safety or efficacy.[255] Compounding the problem, once a device is in use it is difficult to recruit people to a clinical trial in order to evaluate it, thus, making it difficult to generate the required evidence later.[76] Furthermore, manufacturers are likely to be slow to generate additional evidence when they have already secured reimbursement, because evidence generation is a costly process that is unlikely to provide competitive advantage and may result in their device being delisted.

Perhaps worse still, is the subliminal messaging that improves the image of observational data – calling it real makes it appear more valuable and trustworthy, whilst other data is less so, because it is not 'real', thus, undermining the perceived value of RCTs and falsely reassuring stakeholders as to the quality of the evidence base and further preventing public outcry.

6.3.2. How this has influenced the thesis

Initially, WHO's framework for developing policy interventions for medical devices appeared to be the most appropriate choice for guiding a review of lifecycle processes. This was based on the fact that it is policy-orientated, focusses on the key stages that impact patient safety, is specifically applicable to medical devices, and is flexible in that it is not overly prescriptive regarding what to include whilst still giving direction regarding key stages. However, as the research progressed[i] it became clear that the single key pre-clinical process with the most influence on medical device-related patient safety is the regulatory process. Consequently, the planned research on processes was put on

[i] This study was conducted in tandem with the other studies, including the study exploring the lifecycle processes. During the research I conducted for my national placement and also from the research that I was involved with at the KCE (which began during my international placement in September 2019) I found that HTA and procurement are constrained by the lack of evidence available to make their assessments for informed decision-making. Therefore, although I explored these processes in depth, they are not part of this thesis, because the key processes influencing medical-device related patient safety are those related to regulation.

hold[i] and I have concentrated instead on expanding the depth of analysis for this study and conducting an in-depth documentary analysis of the regulatory process. Nevertheless, the next chapter provides an overview of the medical device design and manufacturing stages, focussing on the design controls and the risk assessment and management processes that regulators impose on manufacturers.

6.3.3. Limitations

This review has certain limitations, firstly, is not an aggregative systematic review, so models exist that have not been included. Nevertheless, by including a large sample from a broad variety of sources and perspectives this review provides a reasonable picture of the general form and content of lifecycle models being used. Due to the broad inclusion criteria many of the included models are not intended specifically for medical devices, however, this heterogeneity facilitated a rich exploration of each discipline's perspectives and motivations. Another limitation lies in the categorisation of the models. Most of the categories had overlapping boundaries and many were not mutually exclusive, which means that decisions regarding categorisation were subjective. As far as possible, I tried to introduce consistency by writing descriptions for the main categories and repeatedly questioning my reasoning for placing a model in one or another category, but others may have made different decisions with the same information. Nevertheless, the identified themes are more generally observed patterns in the data and exist independently of how models were categorised.

6.4. Conclusions

In this review I have shown that the concepts of 'medical device lifecycle' and 'lifecycle evaluation' have different meanings, and different purposes for different stakeholders, and that there are certain assumptions and implicit messages underlying these concepts that are reflected in the diverse range of models used for lifecycle evaluation. The general lack of available data for medical devices means that the assumptions underlying the drivers to innovate and adopt innovations remain hidden and cannot easily be validated or challenged. These tacit assumptions and reinforcing messages conceal risks to patient safety that arise from the fact that not all innovations are better, indeed many are worse, whilst rapid access increases the number of people exposed to potentially harmful effects, and a regulatory lifecycle approach is taken that defers evidence generation to the post-market phase in which regulators have little power to

[i] By this time, I had conducted grey literature reviews and several interviews with key informants. Since I obtained ethical approval for these, I still hope to complete that study at some stage after submission of this thesis.

remove a device from the market, further exposing greater numbers of people to harm.[309,323]

The pro-innovation/adoption biases evident in the models illustrate the significant pressure that is placed on HTA, Procurement, clinicians, and even patients, to adopt devices as early as possible. Yet, it is precisely because regulators have adopted a lifecycle approach that there is so little clinical evidence available for clinical and reimbursement decision-making.[309, p.824] If HTA succumbs to this pressure of adopting a lifecycle approach to evaluation, particularly by recommending early access and adoption of 'innovations' on the basis of limited evidence with the promise of later evidence, it may result in the necessary evidence not being generated early enough in the lifecycle, because manufacturers then need very little evidence to secure reimbursement.

Furthermore, although innovation is costly, it can reap large rewards for investors, particularly with a strong pro-innovation and pro-adoption bias that lends itself to the acceptance of devices on the basis of promise rather than evidence of benefit. Yet, the aim of innovation isn't always to improve patient outcomes, innovation isn't always new, and it isn't always better. Incremental innovations frequently have little or no data to support claims of safety and efficacy, though they are more readily granted admission to the market, and more easily enter healthcare systems, where their innovative nature (and lack of supporting evidence) is not clear, because such innovations are generally considered to be the same, only better.

Consequently, adopting a lifecycle evaluation approach for reimbursement decision-making may have unintended consequences, adversely impacting evidence generation and patient outcomes. To counteract this the HTA community could become involved in setting up systems for rigorous and systematic data collection and analysis of patient outcomes within healthcare systems for the highest-risk devices.[275] Regulators are constrained to remain silent when they know that some devices are not as good as others, yet it should be possible to have greater access to non-confidential incident report data. The competent authorities who do make incident data available, could make it more accessible to researchers for analysis. Meanwhile, HTA bodies, policymakers, and public healthcare funders should not allow lifecycle evaluation to be used as an excuse for accepting inadequate evidence and should insist on appropriate evidence being made available for reimbursement decisions, as this may be the last defence some patients have against sub-optimal devices.[31]

Clinicians and the public need to be made aware of the lack of clinical evidence available and that 'improved' devices are incremental innovations with possibly no direct clinical

evidence regarding their safety and efficacy. Therefore, clinicians should not rely on the fact that a device is available on the market as a sign of its being either safe or effective and should insist on the evidence for any 'new' implant being supplied to them, and critically appraise this themselves, before deciding to use it on a patient. They would also be well-advised to collect data on patient outcomes for any of these devices, so that they can create their own evidence and base their consent procedures on this if there is no richer source of evidence.

Clinicians and the public also need to be made aware that regulators base their assessments of most devices on a risk assessment and risk management basis rather than evaluating actual safety outcomes. To address this, two policy approaches are needed: better clinical evidence must be demanded in the pre-market phase; and, in the post-market phase, healthcare systems should set up comprehensive data collection systems to systematically collect, analyse, and report on patient outcomes, at the very least, for implantable devices.

7. Key steps in the design and manufacture of medical devices

The focus of this chapter is on the distal processes prior to clinical use. The design and manufacture of medical devices are key stages in the lifecycle of a medical device. The objective of this chapter is to describe best practice for these lifecycle stages, drawing on national, EU, or international guidance, textbooks, and standards appropriate to the specific process.

Guidance may come from a variety of sources, such as legislation, peer groups, professional societies, professional regulators, expert groups, and researchers. Some guidance is developed through consensus methods (e.g. consensus development conferences, Delphi studies, or using nominal group technique), some as an output of research (e.g. evidence-based guidelines or decision algorithms), some as procedures developed over time on the basis of experiential learning (e.g. standard operating procedures) or based on ethical principles (e.g. codes of practice). Others are developed through a regulatory process culminating in legislation. As far as possible, this chapter draws on guidance derived from the most authoritative or relevant sources to the particular context in order to describe how each of these key lifecycle stages and processes either *should* be, or are *expected* to be, conducted.

7.1. Design

An innovative device may be designed by an emerging designer (e.g. a researcher in a clinical or academic setting) seeking a solution to a clinical problem or seeking a clinical use for a technology they've developed. Alternatively, a device may not be novel. It may be an improvement or an alternative version of a device already on the market. These are often designed within a design department by an established medical device manufacturer. Much of the guidance appears to be intended for established medical device producers. Nevertheless, though the contexts (and available resources) vary, the steps in the process are much the same for both.

Jiang (2015) suggests that the design process may be broken down into phases of activity that occur before, during, and after the manufacturing process.[324] Thus, there is some overlap in the design and manufacturing processes. This subsection will describe the premanufacturing activities.

There are different approaches to the breakdown of the design process, depending on the perspective adopted.[325] When viewed from the design or engineering perspective (which are not entirely the same) the focus is on breaking down the design process into stages that involve distinct types of design activities, some of which are clearly defined as stages, others less so. Taken from the business perspective, it is necessary to

incorporate those aspects that are relevant to developing a successful product that is not only safe and effective, but also successful at generating profit, which means considering additional stages in the development of a medical device. This section will look at design from both perspectives.

Furthermore, there are two aspects to the design of a medical device – the design process itself, and the design controls. Design controls include verification and validation of the design process, its production process, and the resultant products. Additional tools to control and achieve good design include systems to manage the quality and risks associated with medical devices through the institution of a quality management system (QMS) and a risk management system (RMS) for their design and manufacture. The design process is described in section 7.1.1, and its controls are described in section 7.1.2.

7.1.1. The design process

The design process is iterative, and with each cycle of the iteration the requirements are specified in greater detail. It starts with broad concepts and iteratively narrows to more specific and detailed conceptualisation until the end product is finally realised.

Figure 7.1 provides an overview of the process for designing a medical device itself. In addition to this, the design process also includes the design of the equipment, processes and production system required to produce the finished product. Those design processes follow a similar pattern of design as that for the device.[326]

In broad terms these design activities may be described as: identifying user needs; specifying the design requirements (requirements capture); task clarification; and generating ideas (concept ideation or concept generation), all of which make up the *conceptual design* stage. If the project is considered to be feasible, the conceptual design moves into *embodiment design*, then *detailed design*, which is transferred to production once it is finalised. In addition to the design activities shown in the Figure 7.1, there is a stage between conceptual design and embodiment design where the feasibility of the design project is assessed from the business perspective.

Each of these will now be described.

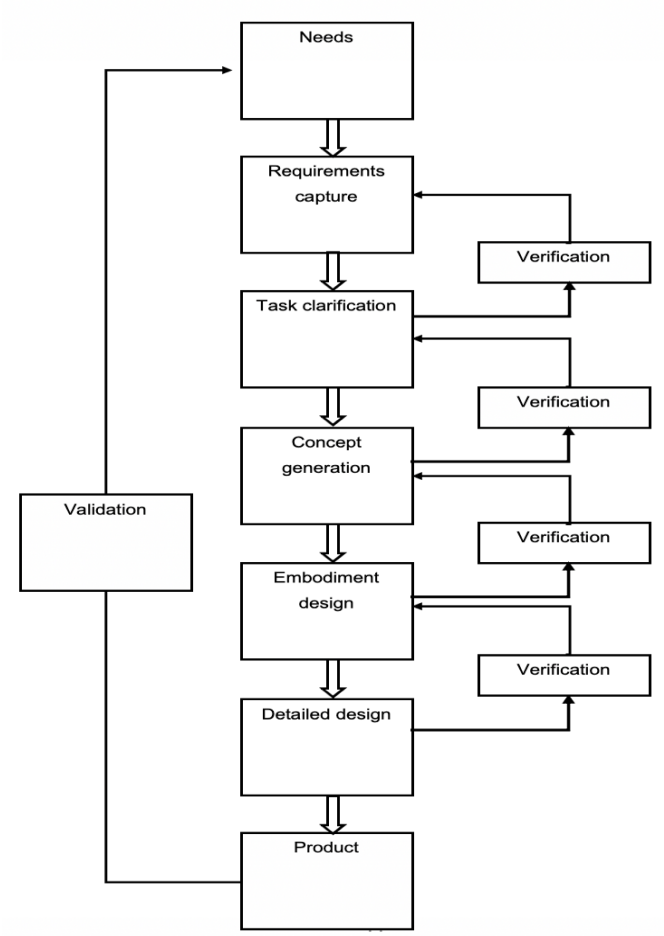

Figure 7.1. The design process (compiled from a variety of sources)

7.1.1.1. Conceptual design

Identifying user needs

The design process usually starts with identifying a problem[i]. Having identified a problem, the next stage is to clearly define what the problem is (*problem definition*) and then to identify what is needed[ii]. Identifying who are the users makes it possible to clarify their needs and the tasks that the device must perform when they are using it. There are different levels of 'user', and the needs of all users must be considered for the successful design of a safe and effective medical device.[326,327] For example, the operators of the device or procedure (e.g. surgeons) are the users, but the 'end-users' are the patients. Other 'users' or stakeholders whose needs must also be met include those who produce, sterilise, package, label, transport, sell, buy, assemble, resterilise, and store the device. Shefelbine et al, 2002, suggest that the problem may be defined by asking:

[i] Although sometimes it may start with the development of a 'solution', for example a new technology is developed and the developer then considers how it may be used or applied to healthcare problems.
[ii] i.e. the requirements.

- Who will use or be affected by the device?
- What must the device do?
- Why will it be used?
- Where and when? [327]

The answers to these questions must be sought from a variety of sources including market analysis, user feedback or complaints, government or industry statistics, medical research literature, and surveys, amongst others, to compile users' needs.[262,327]

Requirements capture

Having identified the users' needs, their specific requirements need to be documented by writing them as a complete set of clear, concise, and specific requirements that are testable, and can be traced back to the reason why they are included (users' need).[327]

Functional analysis involves breaking down the core function of the device into sub-functions and repeating this process until all of the sub-functions are reduced to the most basic steps required to perform that function, which together make up a core function. This must be done without specifying what components or parts are used to achieve these functions. An illustration of how this might be done is provided in Figure 7.2 and Table 7.1 for a hip prosthesis.

Functional analysis enables the requirements to be described as a set of descriptors (i.e. detailed descriptions of the basic functions that the device must have in order to be able to finally do what it is intended to do), which when taken together describe how the device should function and what it should achieve (this process is known as "requirements capture ").

Core Function	**Sub-functions**	**Sub-functions**
Functions like a hip	Supports body weight	Fixed to femur
	Enables sitting	Articulates with pelvis
	Enables walking	Flexes and extends
	Enables bending down	Rotates
Other needs		
Reduces pain		
Improves function		

Figure 7.2: Preliminary functional analysis for a hip implant

Shefelbine et al, 2002, suggest that there are three types of requirements to consider – technical, business, and regulatory requirements.[327] The technical requirements include how the device must function and perform, whilst the business requirements include

cost, scheduling, and any other criteria that impact on the business (e.g. management, reputational, or other requirements).[327] There are also three types of regulatory requirements or standards to consider: those that apply to all products or medical devices (horizontal regulations); those that apply to the particular type of device (vertical regulations); and those that apply to the specific device (product-specific regulations).[327] Shefelbine et al provide a number of approaches and tools to develop design requirements. These include an approach to conducting functional analysis, a requirements checklist in the form of a matrix, and guidance on meeting the regulatory requirements for the EU and the US. The requirements checklist matrix includes considering the process, performance, safety, costs and documentation requirements for the design, manufacture, distribution, installation, operation, maintenance, and disposal of the device.[327]

These specified requirements (i.e. the set of descriptors) then become the '*design inputs*', which are defined as '*the physical and performance requirements of a device that are used as a basis for device design'*, by the FDA Code of Federal Regulations (CFR Title 21, Part 820.3 (f))[i]. [328] Every design input (descriptor) is examined and broken down further to elaborate the requirement in greater detail, the outputs of which are called the design outputs. A design output may be defined as '*the results of a design effort at each design phase and at the end of the total design effort. The finished design output is the basis for the device master record. The total finished design output consists of the device, its packaging and labeling, and the device master record*.'[328] The design outputs include the design specifications for the device, the equipment required, the processes, testing methods (for verification and validation) and the production of the final product.

In addition to specified user requirements, other inputs to the design of the device are drawn from a wide range of relevant sources to include costing and feasibility studies, requirements related to industry standards and harmonised standards, risk control measures, ergonomics[ii], safety features, failure or incident reports, previous complaints, competitor considerations, and features, constraints or information relevant to manufacture, sterilisation, packaging, labelling, transportation or storage.

Each design input must be verifiable, that is it must be possible to measure it in such a way that it is possible to test and verify whether the requirement has been met or not. So for every design input there should be a verification criterion or criteria against which the

[i] Neither the MDD nor the MDR define design inputs.

[ii] This is also known as human factors engineering (HFE)

corresponding *design output* must then be verified. The verification process is described in section 7.1.2.1.

Table 7.1. Hypothetical example of the development of design requirements

Sub-Function	Sub-functions	Sub-functions	Requirements
Functions like a hip	Supports body weight	Fixed to femur	Implant fits into femur
			Implant immobilised at distal end
			Implant surface integrates with bone
			Implant will not become excessively loose over time
		Implant doesn't break under loads within the likely range of human weights	Compressive strength of implant can support 150-200kg
			Torsional strength must be within the required limits
		Femur can support implant without fracturing	Must not transfer forces in excess of those sustainable by a femur within the range of bone compositions experienced by humans
			Must not degrade the surrounding bony tissue

Task clarification

Task clarification overlaps and iterates with requirements capture, in that the aim is to identify all the steps involved in creating and using the device, from design, to manufacture to clinical use, so as to clarify what the requirements are and who must do what to achieve these. Task clarification is considered to be part of the requirements capture process in some guidance, but it is presented separately here to highlight that elucidating the requirements not only requires identifying what the device must do but who must do what to enable this.[327]

Concept generation

The next step is to generate design ideas that might meet the identified needs. This involves taking the functional requirements for the device, (i.e. what it must be able to do), the design features that are required by the end user, and the required technical features, to prepare a number of initial design concepts. Before a new product can proceed beyond the conceptual stage it must be assessed for its feasibility from the business perspective.

Business Feasibility Assessment

Jiang suggests that the *Feasibility Stage* is characterised by four phases: the generation and screening of ideas to meet the identified need, defining the product (product definition), project planning, and project definition review. So, in this representation of the design process, the feasibility stage encompasses the requirements capture, task clarification and concept generation steps described above, but these are presented in a slightly different order, and with a focus on the business-related aspects rather than the design process.[324]

Screening phase

Each idea must be screened against the market forecasts and how the idea fits strategically with these market forecasts, the feasibility of production, and assessment of potential issues that may cause the failure of the project.[324]

Product Definition phase

Ideas that pass the screening phase move to the product definition stage where the characteristics that the product must have in order to meet the end user needs and the business objectives are identified. Cost analyses should also be performed to identify which of several competing ideas best suits these requirements from a business perspective.[262,324]

Project Planning phase

Once the optimum product idea has been selected it enters the project planning stage. This involves preparing a detailed plan of the project (the *project* plan) to identify and describe the tasks, resources, time, and scheduling of activities required to complete the project, which relates to task clarification.

Project Definition Review phase

This project plan is then reviewed (Project Definition Review) to evaluate whether it is worthwhile continuing with the project before finally committing further investment of time and resources. If the decision is to continue, then the product enters the Design and Development stage.

7.1.1.2. Design and Development stage

Once a project has passed the feasibility stage it moves onto the design and development stage. According to Teixeira, it is from this stage on that design controls must be applied.[289] The design and development stage consists of embodiment design and detailed design, which will be described next.

7.1.1.3. Embodiment design

Embodiment design fleshes out the selected concept by developing more detailed specifications, arranging the elements of the device to decide on a preliminary layout, including component sizes.[329] Up until this stage the design is purely conceptual. Embodiment design seeks to answer the questions: How do the physical functions group together into parts? How do the parts all fit together? What are the interfaces and interactions between the parts? What should each be made of? How should they be made? What materials, energy, and information must flow between the component parts, and how is this to happen? What are the design variables? What are the parameters that need to be evaluated? (These could be the strength of a material, flow rates, part sizes, the level of precision and accuracy required, and tolerances, which are the allowable limits for a parameter[i].) What is the best combination of variable values that ensures that the design will consistently produce a product that meets the requirements?[329]

There are three tasks to embodiment design – designing the product architecture, configuration design, and parametric design.[329] The product architecture is how the different functions are arranged together. Configuration design is about a preliminary selection of the materials and the sizes of the different parts that go together. Parametric design is about selecting the final dimensions of the different parts and the parameters and tolerances that must be met.

The descriptors developed during the functional analysis (the design inputs) are used to identify potential materials, parts or components that will meet the requirements of each basic function. These functional requirements must then be mapped to physical components and their specifications (including any interfaces between interacting components) so as to produce a product architecture, which is the preliminary layout of the components or functions.[329] The product architecture is then used to develop a detailed design of the components to be used; the physical properties required of these materials; drawings of the device; production documents; and instructions for use and transport.

The embodiment design process should aim to select the most suitable materials and create the most useful structural form that will deliver the functions required from the device within the design constraints. Materials implanted into the body are called biomaterials, and are defined as: ‘ *Any substance (other than a drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of the system which treats, augments, or replaces any tissue, organ,*

[i] For example, the size may be 1cm and the allowable variation or tolerance might be ± 0.05 mm.

or function of the body.'[330] Biomaterials must be able to '*exist in contact with tissues of the human body without causing an unacceptable degree of harm to that body.*'[331 p, 2941] This ability is known as *biocompatibility*, but the biocompatibility of a material depends on where it is placed in the body since the biological environment varies hugely in terms of its chemical and physical properties and the stresses it experiences or places on a device from one location to another, so that a device may be biocompatible in one location yet not in another.[332] For example, the pH in the stomach is acidic so any device that is placed in the stomach must be able to resist corrosion from acid and the physical or chemical properties that enable this may cause toxicity in body sites that are more basic, such as the spinal canal or the cardiovascular system. So biocompatibility depends on the properties of the material and its interactions with the host at a specific location.[332] Biocompatibility is therefore the '*ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimising the clinically relevant performance of that therapy*.'[331 p.2951]

Therefore, biomaterials must be selected based on their biocompatibility with the host tissue at the intended site of implantation, and their ability to function as intended at that site, without unacceptable degradation in material composition or function for the timescale that it is intended to be in situ. So, biomaterials must be assessed for their effects and interactions at the intended body location and for their intended function. This is done in several ways. The material properties assessed (or known from previous research) include the properties of the biomaterial in general (called bulk characteristics), the properties at the implant surface (called surface characteristics[i]), and its interface with the intended implantation site. These characteristics include the strength, chemical composition, surface composition and topography (hardness/softness, consistency, smoothness/roughness), toxicity[ii], oncogenicity, genotoxicity, degree of interaction or integration of the implant by the host, and blood compatibility.[333,334] The biomaterial must be assessed for the *type* of strength (tensile, shear, compressive, or/and torque) required for its intended application, for example orthopaedic and dental implants have to survive

[i] Surface characteristics are important because the surface interfaces with the host tissue, and interactions at the surface are important determinants regarding whether the implant evokes an acceptable host response or causes harm through degradation, erosion, leaching of ions, and concomitant toxicity, mutagenicity, or unfavourable immune reactions.[333,334]

[ii] The toxicity is the degree of lethality to the cells that it will be in contact with and its effects on their metabolism. Lethality is usually measured in terms of the required dose to kill 50% of the cells. This is called LD50.

significant compressive forces, whereas pacemaker leads require tensile strength, and vascular grafts need to survive shear forces.

The assessment of biomaterials involves a broad range of types of test. Testing may include in-vitro, ex-vivo, in-vivo and mechanical tests to assess strength, functional performance(s), toxicity and potential host-material/implant interactions, such as changes in pH, oxidation levels, implant corrosion, leaching, and the potential for tissue adsorption or tissue degradation. In-vitro tests are performed outside of a living body. Ex-vivo are also performed outside the body, but use tissues or cells, usually from established and standardised cell lines, to assess the level of toxicity of the implant material on the type of cells that the device will be in contact with once implanted. In-vivo tests are tests performed on living organisms (animals) that sufficiently resemble the intended host or host location in terms of physiology or mechanical stresses to assess toxicity and proof-of concept (i.e. does it work in this species?).[333,334] Blood-device interactions must also be assessed in addition to testing the effects on the cells of the intended implantation site as most devices come into contact with blood. Interactions to consider include the effects of the device on the blood (e.g. does it cause clotting) and the effects of the blood on the device (e.g. does it affect surface topography).

7.1.1.4. Detailed design

Having determined the biomaterials and components, and their arrangement within the device, a prototype is developed, though this may be developed in the embodiment stage with further development in the detailed design stage. The reliability of the prototype and each of its iterations should be assessed, and improved through the use of a variety of tests, experiments and statistical analyses designed to estimate and optimise the reliability of the device.[335] Some of these tests include testing-to-failure, testing in extreme environmental conditions, testing to the extremes of the design limits, accelerated life testing, and root cause analysis of the resultant failures.[324] To improve reliability and to reduce the probability of failure, stress-strength analysis is also conducted - this helps to identify the optimum design configuration.[324,336]

Another feature often incorporated into the design process is redundancy design.[324] Redundancy design can be used to increase the lifetime of a product. It involves incorporating redundancy by using multi-component parts instead of the equivalent single component in order to reduce the stress on a single component working full pelt, or else provide standby components that kick into action when the working component

fails (cold standby[i]).[324] This is less useful as a strategy for prolonging the life of implantable devices that primarily have a structural function, with minimal mechanical parts.[324]

The design is further improved through a process of '*reliability growth'*.[324,335] This involves repeated testing, analysis and modification of the design or/and the engineering process until the reliability reaches an acceptable level (known as the acceptance limits).[324,336] Each part or component varies in its properties and dimensions, the objective is to limit the variability of each parameter within a certain range (which is frequently set in the relevant international or EU standards for that component or device).[324,336] Booker et al, 2001, warn that '*variability can have severe repercussions*', as it is a significant source of product failure.[335]

The range of acceptable variation is called the *tolerance*, whilst *tolerance analysis* is the general term for studying the potential accumulated variation in mechanical parts and assemblies. There is variation in everything. Variation that can affect a design can be in a physical dimension, physical property, a measured value, a system, or physical space (including between two parts). The lower the tolerance the greater the precision. *Tolerance stackups* or *tolerance stacks* are used to describe the problem solving process in mechanical engineering of calculating the effects of the accumulated variation that is allowed by specified dimensions and tolerances.[337]

Tolerance is an important concept. Once a project, device, process, assembly or components are within the accepted tolerance (accepted limits of the relevant property, dimension, value, space, etc.) then it should work - whereas outside of those ranges of allowable variation there is a higher probability that it will fail in some way.[324,335] These limits are in a sense arbitrary, but the narrower the acceptable range for each individual tolerance that is set (i.e. greater precision) the narrower the overall range of variation will be, and the higher the probability that the product will work as intended according to the design. However, achieving greater precision comes with higher costs, and so a balance needs to be achieved between improving precision, and thereby product quality, and keeping costs of production low. Generally, international standards should be used to guide the selection of these tolerances, (e.g. ISO, EN, and ANSI standards[ii]).

In addition to these improvements in design, to further improve the reliability of the device it is also beneficial to design a comprehensive and systematic preventive maintenance

[i] Warm standby is when the working component is working at full strength, and the standby components are working at half or reduced strength, but can be called up to full strength when the main working component fails.[324]

[ii] International Standardization Organization, European Norm, and American National Standards Institute

program that specifies what needs to be done, and when, in order to prolong the life of the device when in use.[324] However, this is of less relevance to most implantable devices. Quality and reliability are key features required of the design and development of medical devices.[324] The design process should incorporate quality assurance activities similar to the plan-do-measure-act quality improvement cycle or the clinical audit cycle. Every element should be designed, tested, analysed and fixed (redesigned) until it is refined to meet the requirements.[324]

The design process not only involves designing the device, but it also requires designing the equipment, processes, and the overall production system required to make the finished product. The production system encompasses the manufacturing process, sterilisation, labelling, packaging, preparation of instructions for use (IFU), training (if appropriate) and any training materials or manual, as well as the methods for safe transport and storage of the device, and if required, instructions for preparation for reuse (e.g. cleaning, re-sterilisation, and repackaging).

The design of the equipment, processes, and production system follows a similar design process to that of the design of the device. These design processes may also be broken down into similar stages of identifying user needs (where the 'users' here are those conducting one of the production processes), specifying their requirements, generating design inputs, and 'designing' to produce design outputs, which must be verified, and the final outputs validated.[326]

7.1.1.5. Design Review

The final step in preparing the detailed design is the design review. '*Design review means a documented, comprehensive, systematic examination of a design to evaluate the adequacy of the design requirements, to evaluate the capability of the design to meet these requirements, and to identify problems.*'[328] Once this is successfully completed (including successful completion of all the required verification and validation tests), the design is transferred to the manufacturer or production team.

7.1.1.6. Transfer to production

Transfer to production involves transferring all the design documents, drawings, schematics, test reports, final design review report, and plans for the equipment, processes and production system to the manufacturer or manufacturing team.

7.1.2. Design Controls

7.1.2.1. Verification and Validation

Verification is the process of checking that design outputs match the **design inputs**, that is the outputs from the design meet the specified requirements as stated in the design inputs. The design outputs from one cycle of design activity become the design inputs to the next. Verification ensures that the design process is proceeding as intended so that the end product is what it was intended to be.

Validation is the process of checking or testing the final output to make sure that it meets the **user needs**. Verification is intended to check that the device is being 'built right' whereas validation is intended to check that it is 'the right device'. [326,327,338]

Verification

The questions to consider when developing the verification criteria for each design input are: What are the requirements? How would we know if these have been met? How can we measure this? What level of this measurement would indicate that the requirements have been met? (This is the acceptance level or acceptance criteria).

In addition to designing the actual device, the design process also includes designing *how* it is made, including the design specifications for each piece of equipment necessary to produce each of the device components, how the processes are configured, and the overall production process. Each iteration in this design process must also be verified to check that the design outputs match the design inputs. To do this a verification plan must be prepared that includes the cut-off values, which indicate when each requirement has been met or not (i.e. that the output matches the input). The verification plan details the tests or observations that must be performed (and documented) to check that each output matches its corresponding input. The verification reports become part of the device's technical file or design history file.

Ward et al, 2002, recommends that the verification process take place in three stages, starting with preparing an outline verification plan, moving on to refining the verification plan, before the final stage of executing the verification protocols developed in the refined plan.[338] As with the rest of the design process this can be broken down further into smaller steps, which are also iterative. These are summarised in Table 7.2.

Validation

Validation is required to test if a device meets the needs of the intended user. Alexander et al, 2001, focus on the validation processes for designing the medical device, the process equipment development, and the production system, asserting that '*The*

development of validation requirements should commence as soon as the user needs are known.'[326] They suggest six tactics to employ to support design validation:

1. Capture implicit and explicit requirements
2. Check that requirements are verifiable
3. Use a risk-based approach to design and verification
4. Consider the effects of redesign on requirements
5. Consider the effects of device requirements, design, and verification of process requirements, and validation
6. Consider the effects of process redesign on device requirements

Table 7.2. Verification planning process, adapted from Ward et al, 2002.[338 p.30-31]

	Process (activity)	**Outputs**
Stage I - Outline verification plan		
Step 1	Review requirements and outline protocols	Verification protocols
Step 2	Assess risks	
Step 3	Draft verification plan	Verification plan
Stage II - Refine verification plan		
Step 4	Determine verification demand	
Step 5	Review candidate verification methods	Verification protocols
Step 6	Assess benefits/limitations of each methods	
Step 7	Select preferred approach	Verification plan
Step 8	Validate selected method	
Stage III - Execute protocols		
Step 9	Complete protocols	Verification protocols
Step 10	Carry out protocols	

338 p.30-31

Table 7.3. An example of a Technical File (Design History File) Trace Matrix document that is used to trace the design process, extracted from a presentation by Dimitri Sheremetiev to NCAD students March 2019.[339]

Who? User or Stakeholder	Needs		Design inputs		Design outputs		Verification		Validation	
	Need	Why? Source	Design input	Why? Source	Design output	Why? Source	Test	Acceptance criterion: evidence report	User studies	Acceptance criteria: evidence report
User A										
Stakeholder 1										
User B										

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7.1.2.2. Quality Management System (QMS)

Keeping track of all the design cycles and their documentation is essential to ensure that the design process proceeds in such a way that every output can be traced back to its corresponding input and verification results. This requires a systematic approach to managing documentation in the form of a quality management system (QMS).

A QMS is defined as '*a set of policies, processes and procedures that help an organization meet the requirements expected by its stakeholders. It is based on the Plan-Do-Check-Act cycle, a four-step management method used in business for the control and continual improvement of processes and products.*'[340]

The harmonised standard EN ISO 13485 provides guidance to manufacturers of medical devices regarding what must be included in a QMS. Its application is a legal requirement for high-risk medical devices in many jurisdictions, including the EU.

A QMS must include attention to:

1. Meeting the documentation requirements
2. Ensuring management responsibility for quality and for an effective QMS
3. Provision and management of resources (human and infrastructural resources) to ensure an environment that is capable of achieving conformity with the regulatory requirements, including control of potential contamination
4. Design controls during 'product realization', to include project planning (including risk management), communication, requirements capture, and planning and controls (including reviews) for design and development, process design and development inputs, outputs, verification, validation, transfer, changes, and control of files
5. Purchasing controls, including the documenting of relevant information, and verification of the purchased product[i]
6. Production and service provision controls, including documentation, qualification of infrastructure, process and product monitoring, measurement of process and product parameters, ensuring equipment for monitoring and measuring is available, ensuring cleanliness, and implementing finishing operations (i.e. labelling, packaging, product release, delivery, and post-delivery activities).

7.1.2.3. Risk Management System (RMS)

Manufacturers of medical devices are required to institute a risk management system for their production process, and, in the case of medium to highest risk devices, the design

[i] For example, tests to ensure the purchased products/components are of sufficient quality.

process. A risk management system is a *'set of elements of an organization's management system concerned with managing risk'*, which may *'include strategic planning, decision making, and other processes for dealing with risk'*.[341] Furthermore, '*the culture of an organization is reflected in its risk management system'.* [341]

According to EN ISO 14971:2019, the international risk management standard for medical devices, risk is defined as a '*combination of the probability of occurrence of harm and the severity of that harm'*, whilst risk management is a '*systematic application of management policies, procedures, and practices to the activities of communicating, consulting, establishing the context, and identifying, analyzing, evaluating, treating, monitoring, and reviewing risk*.'[342]

Risk Management Process

Harm is actual damage or injury, whilst a hazard is something that has the potential to cause harm, and a hazardous situation results when a combination of a hazard and a particular set of circumstances or sequence of events create a context where there is a potential to cause harm.

The risk management process involves the assessment of risks and the application of control measures adopted for the identified risks. The risk assessment process is broken down into two parts - risk analysis and risk evaluation. *Risk analysis* involves identifying the hazards associated with the device at each stage in its lifecycle, starting with a preliminary hazard analysis on the user needs.[326, p.34] This means specifying the intended use, (including foreseeable unintended uses, or future potential uses), and considering how the device could affect safety in those circumstances. For each hazard, consideration must be given as to how it can lead to a situation where it might cause harm, and what kind of harm it might cause. These hazardous situations must then be explored and the level of risk attributed to each must be estimated - *risk estimation*, based on the probability of occurrence of harm and the likely impact or severity of that harm. These risk estimates are then evaluated to decide if each risk is an acceptable one or not, this is *risk evaluation*. If a risk is not acceptable it must be removed or, failing that, lowered to the lowest practicable level of risk: firstly, by using inherently safe design and manufacture; secondly, by incorporating protective measures in the device or the manufacturing process; and thirdly, by providing information, and if appropriate, user training. These are the risk control options. Each control must be verified to make sure that it has worked. The risks are revaluated after the controls have been put in place, and the residual risk is estimated for each to evaluate its acceptability. The total residual risk is also evaluated for its acceptability by conducting a benefit-risk analysis, which

compares the anticipated benefits with the residual risks to determine if these risks are acceptable in light of the hoped for benefits. The risk management process is illustrated in Figure 7.3.

The risk management activities must be recorded in the device specific risk management file of each device type. Tools for analysing risk include Fault Tree Analysis (FTA), Failure Mode and Effect Analysis (FMEA), Failure Mode, Effect and Criticality Analysis (FMECA), Hazard Analysis Critical Control Points (HACCP), and Hazard and Operability Study (HAZOP).[269]

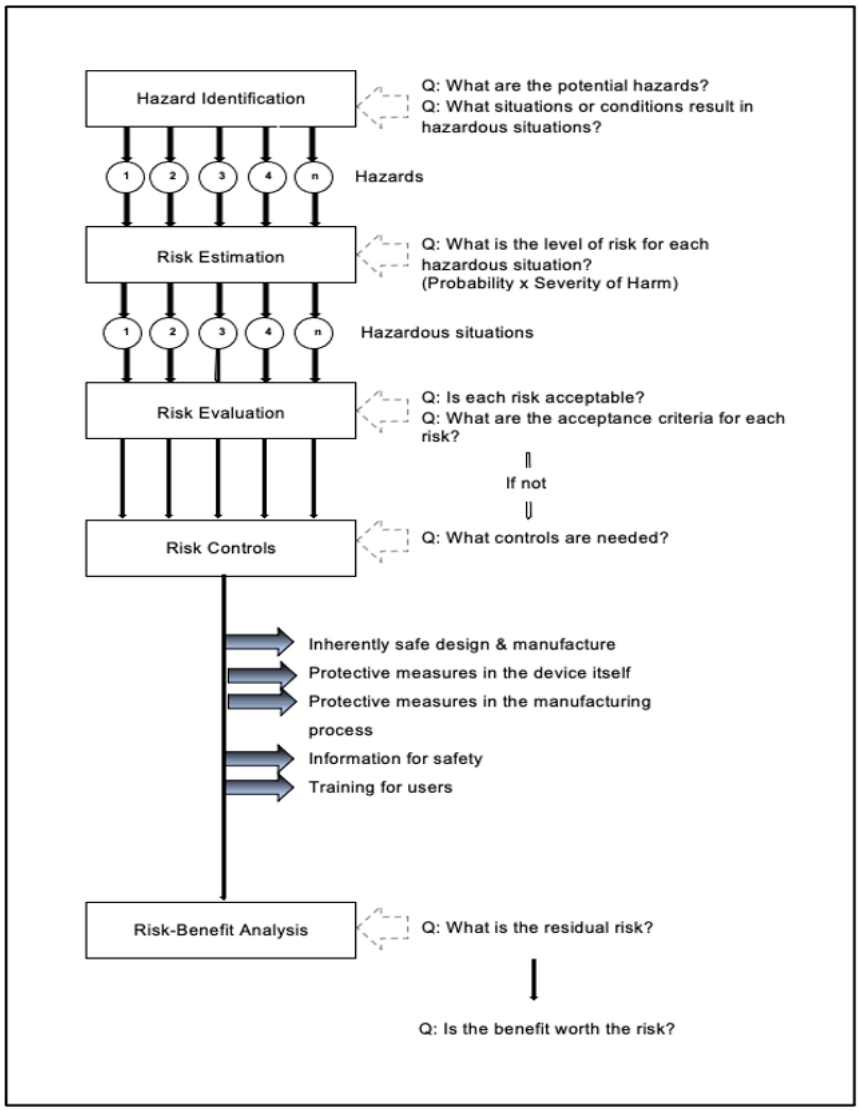

Figure 7.3: Risk management process

7.1.3. Medical device design from a business perspective

Teixeira focuses on the business side of design control, and asserts that '*the main objective of any business is to make money*' and argues that *'the prime design criterion is whether the device will make money*'[i].[289 p.9-10] Consequently, she considers a number of questions related to the business side:

1. Is the product viable?
2. Will anyone buy it?
3. Is it reimbursable?
4. Does the device fit with the company's business strategy and the overall product portfolio?
5. Can it be manufactured at a cost that will provide the desired margin of profit?[289 p.10]

In addition to the previously described phases of design, Teixeira suggests that there is another phase – improvement and optimisation, and recommends that:

'In Phase 5, you should be looking at ways to optimize your process and improve your product or device. Your customers' feedback, good or bad, should always be sought for improvement opportunities. Look at what your competition is doing. This information needs to be continually evaluated and fed back into the design control process so that improvements can be made. Technology changes so fast that it is essential that you look at new and better or cheaper ways of doing things. For example, look for ways to improve process efficiencies in order to decrease cycle times, delivery times, and overall costs and improve product or device quality, thereby decreasing product failures and rework costs.'[289]

This pressure to improve is actually a risk in itself as any changes to the inputs or outputs in the overall design process may not work if they are not adequately verified and validated.

However, Figure 7.4 extracted from the NASA Systems Engineering Handbook Rev 2, illustrates how the design (and manufacturing) costs are locked into a product early in its development process, and the extremely high cost of introducing design changes later rather than earlier in its development, demonstrating how important it is for firms to get the design right as early as possible and the importance of paying attention to capturing all requirements and applying design controls. It also shows how much of a disincentive

[i] She suggests that engineers '*have not been hired to make the longest lasting, strongest, most cosmetically pleasing medical device. They have been hired to make a medical device that is safe and effective for the application for which it is intended to be used. More important, they have been hired to do this and generate the most profit.*'[289 p9-10]

exists to change a design (or possibly even to identify the need for a change) if the product is close to launch.

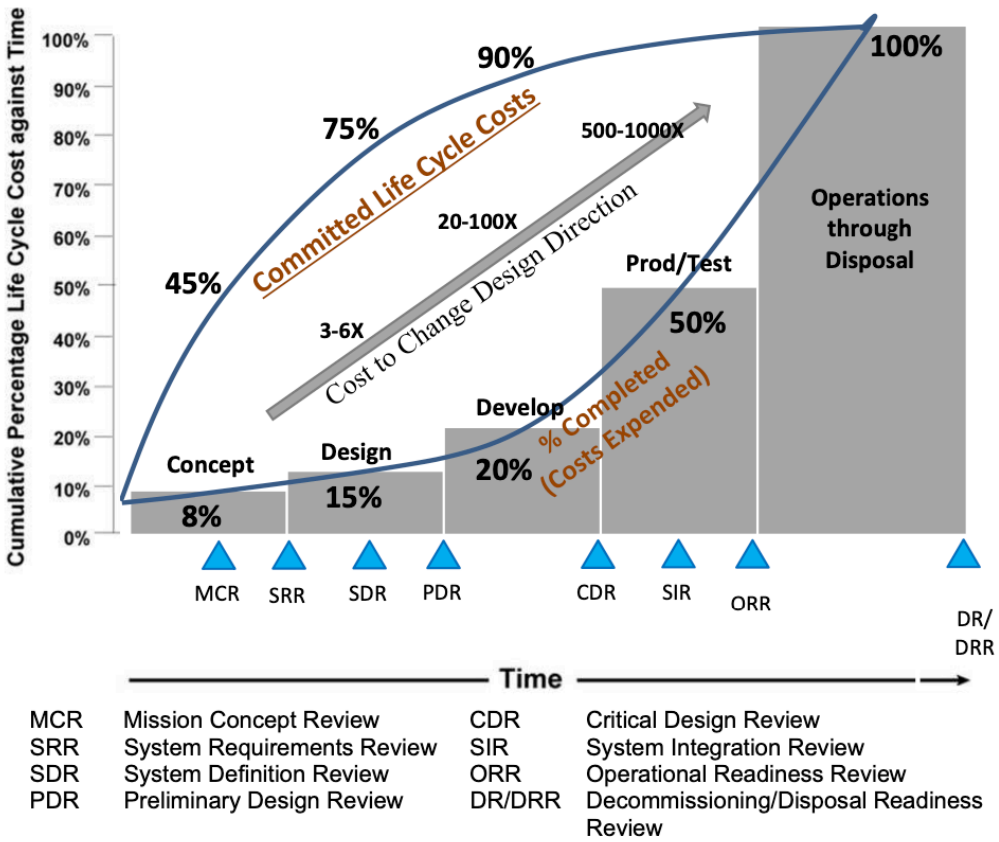

Figure 7.4. Life-cycle cost impacts from early phase decision-making[i] - Extracted from the NASA Systems Engineering Handbook Rev 2, Fig.2.5-1.[268 p.13]

7.2. Manufacture

Once the detailed design has been verified, validated, and reviewed, the 'final' design, in the form of the design history file (or technical documentation or design dossier), is transferred to the manufacturer to enter the production stage.

The aim of production system design is to achieve the best balance between production costs, production levels, and the quality of the product being produced.

Designing a production system requires designing the layout and interaction between the components required to produce the product - that is the raw materials, components, expertise, equipment, and workflow necessary to convert raw materials into the finished product. There are multiple steps and parts involved in the production of a completed product, each with its own production process, which together make up the production system.

[i] Each triangle represents a review of the project to date, whilst several also act as 'stage-gates' in that they represent decision-points regarding whether to continue or to discontinue the project.

There are different approaches to the production process which a manufacturer needs to take into consideration in choosing a production system design. For example, there are three main types of production system designs: 'Job Shop Production'; 'Batch Production'; and 'Mass Production', each with its own advantages and disadvantages. The different characteristics of these are described in Table 7.4 in terms of type of equipment used, the production volume, typical type of product produced, skills required of the workforce, degree of system complexity, and typical costs involved.[324] It shows that the different factors that need to be considered in setting up the production system include the skills and number of workers required, the cost of the equipment and the cost of changing set-ups, degree of mechanisation, productivity level required, the complexity of the system and the need for flexibility versus predictability and stability. These need to be balanced to succeed in meeting the business objective of making profit.

324 p.15-18

Table 7.4: Characteristics of the three types of production systems, based on details extracted from Jiang 2015.[324 chapter 2, p.15-18]

Production characteristics	Job Shop Production	Batch Production	Mass production
Equipment	General purpose; flexible	General purpose; specially designed jigs and fixtures required for different batches	Highly specialised
Production volume	Low volume	Minimum volume lot	Large production volume
Product	High variety	Moderate variety	Low variety; very specific products
Labour	Highly skilled; workers do a wide variety of tasks from end-to-end for a given product	Skilled work	Low skilled; variety of possible jobs; supervision and minute division of labour
System	Complex; little repetition	May be complicated but routine; repetition of production order	Highly mechanised production line; repetitive tasks
Cost	Expensive	Medium cost	Low cost
Examples of when this type of production process is favoured	Tooling (i.e. manufacturers who make the tools required by device manufacturers) Custom-made devices 3-D printing		Bandages, stethoscopes, Medical device accessories, such as tubing or connectors

7.2.1. Production System Design

Key elements in the design of a production system include supply chain design; production planning; specification process; selection of the required equipment and tools; and the design of the layout of the factory floor for the optimum flow in the production process.

7.2.1.1. Supply chain design

Designing the supply chain to optimise the production process involves identifying and evaluating the different options available regarding supplies, transportation, warehousing, stock control, stock flows, and the management of these in order to identify the best combination in terms of cost and impacts on quality and price (performance).[324 p.17] Raw materials and components not manufactured on site must be sourced at the right time and in the right quantities (and quality) from the suppliers. Supply chain management is a complex decision-making process with multiple competing demands. Selecting the best combination of suppliers, transport and stock control (inventory management) in order to reduce the "total supply chain cost" is the aim. The decisions are influenced by the costs (direct costs, transportation, storage or warehouse costs, and the prices of materials and components), quality, and timing requirements, amongst other things. Sourcing the right materials, at the right time, quality, and price in order to keep costs low, whilst ensuring sufficient productivity and quality products requires good supply chain design and management.

7.2.1.2. Production planning

This involves planning the production process, assessing the tolerances for the product and the process, and developing process capability indicators, which are a means of predicting the performance of alternative production systems being considered. The "design parameters" of a production system that need to be considered, amongst others, include flow paths, the overall capability of the process, the number of workstations, the buffer size, and the number and type of inspection or testing stations.[324 p.17-18]

For Job shop production systems and Batch production systems, factories frequently produce more than one product, so the production process must be set up for each different product. This needs to be planned so that the production set up time is minimised and the production workflow is optimised by arranging the sequence of set-ups to ensure easy flow, high quality and productivity. Mass production may not require repeated production set ups but planning the production process to ensure optimal productivity, timely workflow and quality outputs is still essential because it is generally

highly mechanised and less easy to change once set up, so it is important to optimise this from the beginning.

The manufacturer or designer must juggle the oft competing demands of production quality with system flexibility, as manufacturing plants often produce more than one line of products. The system that is flexible enables greater capability for higher levels of production of a greater variety of products, but this may impact on quality, particularly if the production process is a complex one involving a large number of parts, different types of processes, a large variety of products, or unpredictability in the scheduling of the different manufacturing processes. The optimum layout of the production system to ensure sufficient flexibility and robustness in the production process is crucial to producing quality products.

Similar to analysing tolerances for the design of the device, manufacturing tolerance analysis should be conducted to assess the combination of processes that must fit within the acceptable limits of variation in the manufacturing process to produce the minimum acceptable number of product failures[i].[324 p.17, 228]

The equipment to be used in the production process should be selected on the basis of its reliability and its operating characteristics, such as temperature, speed, pressure, et cetera, which involves making trade-offs between the quantity and quality that the equipment can produce. Machine 'Failure' in this context may be operational, that is the machine breaks down, or it may be a quality failure, where the machine produces defective parts or products.

All of these factors should be taken into account when designing the manufacturing process and should be written into the process design specifications.

7.2.2. Quality control system design

The quality of a device depends on how closely it meets the design specifications regarding its physical attributes (e.g. size, weight, shape, etc) and functional abilities (e.g. strength or weight-bearing capacity, conductivity if electrical, etc).[324, chapter 12] The design specifications are expressed in quantitative terms, which means that they can be measured and products can be assessed regarding their compliance with the specifications. There is always variability, and the notion of tolerance allows variation within a very precise range of values, but if the degree of variability is large it is likely to result in more product failures, whereas a narrow degree of variability enhances the

[i] i.e., the lowest acceptable proportion of product non-compliance or non-conformance at final inspection or testing.

average likelihood of device survival. Therefore, quality controls are needed to ensure the lowest level of variability in the end-product and in the production process.
There are four approaches to setting standards and testing against those [324, p.19]:

1. Testing outputs against standards
2. Standard quality control of inputs and processes
3. Total production systems, whole system approach to minimise cost and optimise quality
4. Customer quality, meeting customers'' needs and preferences

Quality is planned into the design. Jiang describes three basic quality planning processes aimed at improving the product and the production process.
Quality Function Deployment (QFD): This captures the customer's requirements, breaking them down into required product attributes. QFD is used to design the product and feeds into the production process design by identifying any additional requirements for inclusion.
Design of Experiments (DOE): The design of experiments uses experimentation and statistical analysis of the results to identify the optimal combination of operating factors that will best achieve the desired product. Operating factors are those variables that a manufacturer can control during the manufacturing process, such as the speed, volume, temperature, pressure or flow rate of a manufacturing process or piece of equipment.
Failure Modes and Effects Analysis (FMEA): This analysis can be used to identify which is the best option between a number of alternative manufacturing processes by analysing the failures and their effects and the resultant risks for each.

There are also three levels of quality control – quality control of the inputs, the process, and the outputs.[324 p.19-21]

7.2.2.1. Quality control of inputs

Acceptance sampling is batch testing of supplies using a sample from each batch to determine whether to accept that batch from the supplier or not. Acceptance sampling has to be balanced with the cost of testing, but it improves the probability that the final product will meet the required standards and conform to the design specifications.

7.2.2.2. Quality control of process

Controlling the quality of the production process requires quality controls and inspections during the process, including inspecting components and final products for quality.
Inspections have to be planned into the production process to specify where to put the inspection stations, how many inspection stations, at which stage in the process, how

often, and what to do with those outputs that don't reach the required quality level (called non-conforming or nonconformances). These factors are influenced further by the system layout, space, time required for inspection, the average acceptable quality level, and budgetary constraints.

Statistical process control involves specifying the acceptable level of fluctuation in the values of controllable process parameters (such as operating speed, temperature, et cetera) in the production process.[324, chapter 14] These parameters are measured regularly and the results are recorded on a process control chart (Shewhart control chart) which is used to assess whether a process is in or out of control.[343] A process that is "out of control" has exceeded the acceptable level of fluctuation, signalling that the production process needs attention (such as the recalibration of the machines, or resetting the values, or the timing, or retraining personnel, etc) because the end products have a higher probability of failure.[343]

Greater process variation introduces more error into the process. If the fluctuation is readily apparent, then it can be dealt with immediately, but trends are generally only detected using process control charts. It is possible to detect a change in input parameters in batch production more readily than in continuous production. Optimising the batch size to reduce set up costs, whilst not overly increasing the proportion of products that don't meet the required quality level involves balancing these two factors (cost and quality) to minimise unit cost. Increasing controls increases costs and reduces productivity. So, there is also a balance to be struck between testing (and statistical control) and productivity.

7.2.2.3. Quality control of outputs

Output controls generally take the form of quality inspections, screening, and testing of components and final products.[324, chapter 15] These are needed as the reliability of the end-product depends on the quality of its component parts and the manufacturing process variability. Variation in either of these will produce products of varying quality, reducing the reliability of the end-products and a higher chance of product failure. The point of screening is to remove defective devices from a production run before they are put on the market.

Quality screening methods include burn-in (used for components or devices with electrical components) and environmental stress screening. Environmental stress screening (ESS) is a set of methods to accelerate the ageing of a product,[324, p.273] by exposing it to excessive stresses (such as thermal stresses, vibration, shock, and for orthopaedic devices, tensile, torque, and compressive pressure).

Screening is expensive, but so are '*field failures'* (i.e. devices which fail when in use),[324, p.267] so manufacturers must balance these costs, which they achieve through the use of process control charts and statistical optimization methods for calculating the best balance between testing/screening and the acceptable limits of variation.[324, p.267-9] To do this the screening limits and the acceptance criteria must be set, which is done by determining what level of nonconformance is acceptable (for the end product and for its component parts) balancing the risks and cost of failure in use with the costs of testing (including device destruction).[324, chapter 15] Jiang suggests that nonconforming end-products may be scrapped or reworked to bring them up to the required standard, which again depends on the relative costs of reworking versus scrapping. [324, chapter 13]

7.3. Discussion

The design and development processes are complex, requiring fastidious document control to manage the quality controls, and the verification and validation processes, hence the requirement for a QMS. Similarly with the production and final testing/inspection processes.

All of these approaches to design and production focus on improving the quality of the product and its reliability. This is because high quality devices are less at risk of failing and are less likely to cause harm due to their unreliability or failure. However, being of high quality does not automatically mean that a device is clinically effective or safe. High quality devices may yet be ineffective at treating a patient's condition, and they may also cause harm despite being of good quality.

The risk management process is intended to reduce the risk of unacceptable harms occurring. Nevertheless, the focus is on the ex-ante risk of these occurring, rather than on determining the ex-post rate of occurrence. Furthermore, it is the manufacturer who determines the level of risk of each potential adverse outcome from occurring and it is the manufacturer who decides what is a considered to be an acceptable rate.

7.4. Conclusion

This chapter has provided a description of some of the processes involved in the design and manufacture of medical devices and the process controls that should be applied to them to ensure the quality of the device produced. This provides the necessary background to understanding what it is that regulators attempt to control and some of the means that they use to do this. It demonstrates that the focus is on reducing the potential risks and improving the reliability and quality of devices

8. Regulatory institutions and regulatory policy influencing medical device regulation in the EU

The research question that this study sought to address was:

RQ2. How are medical devices regulated? And how does this affect patient safety?

However, as previously explained, regulation occurs at multiple levels. It also changes over time. My approach to answering the research question has been to subdivide the findings into three chapters. This first, Chapter 8, addresses the institutional actors involved in medical device regulation, globally and at the EU-level, and their regulatory policy. The second, Chapter 9, explicates the EU legal frameworks for medical devices, whilst the third, Chapter 10 explores its implementation and outcomes. The findings from these are further explored in the Discussion chapter.

This chapter begins with a description, in Section 8.1, of some of the supranational actors and key policies influencing medical device regulation in the EU and its member states[i]. This is followed by an explanation of 'State intervention' as it was applied in this study, in Section 8.2, where I describe the history of the EU regulatory institutions. Then I describe the legislative procedures that they must operate under, how they evolved, and how they were applied to medical devices in Section 8.3.

8.1. Supranational Intervention

At the supranational level the goal is frequently to standardise processes that affect trade, primarily economic and legal requirements. Economic requirements generally relate to the removal of the imposition of embargoes, restrictions, or quotas on goods imported from foreign countries designed to protect domestic producers. Legal requirements relate to specific rules applicable to particular types of goods, usually specifying a certain level of quality and safety, corporate governance, or rules governing the public procurement of that type of good.

Regarding medical devices, many countries regulate market entry to ensure a certain level of quality and safety of the devices entering their healthcare systems. These

[i] The specific interest of this study is on how non-active implantable medical devices are regulated in Ireland, however, since the EU determines the legal framework for medical devices in its member states (MS) this means that medical device regulation in Ireland is derived from EU directives and regulations. Therefore, it is the EU institutions, their regulatory policies, procedures and practices, and their rules that, for the most part, create the legal framework for medical devices in Ireland. In addition, there are supranational organisations that have also had a significant influence on the regulation of medical devices. Therefore, this review briefly explores supranational influences, but it concentrates primarily on the medical device regulatory process from an EU perspective, relating it, where appropriate, to the Irish context for specific detail.

regulations pose a barrier to trade, but most people would not trust devices that have not been checked for their quality and safety, consequently, the removal of regulations would be unacceptable to most people, including industry, who largely depend on consumers having confidence in their products in order to sell them.

However, differences in national regulatory requirements and regulatory approaches between nations pose barriers to trade by making it more expensive and difficult for industry to market their devices in a variety of jurisdictions. Therefore, efforts to remove barriers to trade have focussed on harmonising regulatory requirements, so that they are the same across jurisdictions, reducing the cost and effort required to market products more widely.

As noted previously, in Chapter 5 (Figure 5.14), Cheng recommends that there are seven phases in the life of a medical device that require regulation – the design, manufacture, packaging and labelling, sale, advertisement, use, and disposal of medical devices.[97] Global efforts at harmonising requirements have centred primarily around the first four of these phases.

As a first step towards harmonisation, it is necessary to determine the essential principles, that is the minimum requirements, that are necessary for each jurisdiction to allow access to its marketplace. In order to harmonise these requirements, they must be negotiated between jurisdictions to achieve agreement on a common set of requirements.

The next step is to develop a standard means of being able to demonstrate that these requirements have been and a standard approach for regulators to assess if they have been met. One way to do this, is to set standards specifying the essential requirements, against which compliance can be assessed, then if a standard has been adopted it may be assumed that the product meets the requirements of that standard.

Standards are developed and updated by technical committees composed of the representatives from the disciplines and specialties relevant to the specific standard. This means that industry is intimately involved in their development.

Generally, apart from a few specific ones, standards are not legally mandated, and their use is optional. However, standards are internationally recognised and their use increases confidence that the product is of good quality. Furthermore, they may be used by regulators as a means of assessing regulatory compliance and in some jurisdictions compliance with certain essential requirements may be assumed without further investigation or further requirements being imposed, if relevant standards have been applied. An advantage of using standards is that they can be changed more readily than the law and without requiring changes in national laws, so they can easily be updated

and applied across multiple jurisdictions at the same time when updated. This suits industry and regulators, since changing the law is time-consuming and expensive.

However, standards are not publicly available, they exist behind a pay wall and are confidential even when access is purchased. Consequently, the public cannot see what they refer to, include, require, or don't require.

In fact, standards are deliberately nonprescriptive describing general approaches rather than specific details on the structures or processes that must be set in place, nor do they require specific measurable outcomes to be achieved to meet the standard.

Several supranational organisations have been influential regarding medical device regulation, particularly promoting the harmonisation of regulatory approaches, including the World Trade Organization (WTO), WHO, Global Harmonisation Task Force (GHTF) and its successor, the International Medical Devices Regulators Forum (IMDRF), as well as regional organisations, such as the Pan American Health Organization (PAHO) and the Asian Harmonisation Working Party, amongst others. Each of these has had significant influence on the regulation of medical devices in individual nations. The next subsection will briefly describe some of the supranational organisations, particularly WHO, GHTF and IMDRF, discussing how they have influenced regulatory practice in the EU.

8.1.1. World Trade Organization (WTO)

The WTO is an organisation that is committed to removing international trade barriers, particularly, but not limited to, tariffs imposed by one nation on goods originating from another nation. Claiming that it '*is the only international organization dealing with the global rules of trade*', its main aim is to ensure that trade proceeds freely, smoothly, and predictably.[344] It was established in 1995, but has a longer history as it was the successor to the General Agreement on Tariffs and Trade (GATT).[345]

Initially agreed in 1947 as a bilateral trade agreement between the US and the UK,[346] over the following sixty years the GATT expanded to become a multi-lateral trade agreement with 123 signatory nations, including the EU.[345,347,348] As a result it has a direct impact on the rules that the EU (and its predecessor, the EEC) can impose on imported and exported products, such as medical devices. These rules extend to the procurement of goods by public authorities (e.g. healthcare products procured by the public healthcare service), which must apply the same rules to products of foreign origin as are applied to domestic products.[349, Article IV.5]

8.1.2. World Health Organization (WHO)

In 1946, the Constitution of the World Health Organization was drafted and adopted, establishing the WHO as a specialized agency of the UN when it came into force in 1948.[350] High-level policy and goal setting for WHO is discussed and decided on at its annual World Health Assembly (WHA) with the aim of improving world health through various initiatives.[351] WHO provides advice, guidance, and support on public health issues to member nations via its regional networks, guidance documents, training, reports, and data.[351] One initiative, that is particularly relevant to medical devices, has been the development of policies in a technical series to support nations in the management and safe use of medical devices.[352] These include guidance on national policy-making for medical devices and their regulation, which have influenced the policymaking and regulation of medical devices internationally.[109,108,107,106,353,105,354–357]

More specifically, Cheng was requested to prepare guidelines for the regulation of medical devices, which were published in 2003 and formed the basis of the model regulatory framework, adopted by WHO in 2017, which is intended to guide nations attempting to develop or improve their own legal frameworks for medical devices.[97,108] This was updated in 2022 taking into account guidance published by the Global Harmonisation Task Force (GHTF), the International Medical Device Regulators Forum (IMDRF), and regional regulatory harmonisation initiatives.[172]

8.1.3. Pan American Health Organization (PAHO)

PAHO is a Pan-American health organisation that works with its member states to promote and protect the health of people living in the Americas.[358] It is also the regional branch of WHO for the Americas. One of its influences on the regulation of medical devices globally has been the publication of some of the earliest key documents guiding the regulation of medical devices, including amongst them Eccleston (2001), Cheng (2002), and the Model Regulatory Framework.[359,249,108] These documents directly informed the content of those published by WHO, which has perhaps the biggest direct supranational influence on national health systems.

Eccleston's guide declared that there are eight principles that should be upheld when designing a regulatory framework for medical devices (listed in Box 8.1).[358] Interestingly, although this guide was being produced at about the same time as Cheng's initial guide, both under the auspices of PAHO, this principles approach was not adopted, but rather Cheng's phased approach, as the basis for developing WHO's Model Regulatory Framework.

8 Principles of regulation considered to be the *'cornerstones of an effective medical device regulatory program'*

1. The primary goal is to protect public health and safety.
2. A regulatory system should ensure that valuable new technologies are made available to the clinical community and to patients and consumers expeditiously while preventing unsafe or ineffective devices from reaching the market.
3. Regulatory decisions must be based on strong and clear science, free of external influences and consistent with the directives of law.
4. As the guarantor of public health, enforcement of the law must be vigorously, fairly and uniformly carried out and appropriate regulatory and legal actions taken against violators.
5. Government-prescribed rules and procedures must be clearly articulated for those who must comply with them.
6. Assuring medical device safety entails more than the functioning of the device itself; it requires oversight of the use of medical devices.
7. Information on product risks must be openly communicated with health professionals and consumers.
8. Countries instituting medical device programs should be cognizant of ongoing international harmonization efforts so as to preclude regulatory controls that conflict with actual harmonized rules and guidelines or with the spirit and goals of international harmonization.

Box 8.1. Principles of medical device regulation[358]

8.1.4. Global Harmonisation Task Force (GHTF)

According to Altenstetter, the GHTF was set up on foot of a request from the FDA to industry associations (AdvaMed and the National Electrical Manufacturers Association).[140 p.237] However, this is not mentioned in the official history on its website, which states that the GHTF was founded in 1992 by regulators and industry representatives from the EEC, Canada, Japan, the US, and Australia (who joined the group early in 1993). Its stated objective was:

'To encourage convergence at the global level in the evolution of regulatory systems for Medical Devices in order to facilitate trade whilst preserving the right of participating members to address the protection of public health by regulatory means considered to be most suitable. This is achieved by identifying and developing areas of international co-operation in order to facilitate progressive reduction of technical and regulatory differences in systems established to regulate medical devices.'[360 p. 1-2]

To achieve this goal of harmonisation and regulatory convergence, it initially set up three study groups, later expanding this to five. Each study group (SG) was tasked with a particular remit to further harmonisation. Specifically, these included the investigation of regulatory practices across the five jurisdictions, design practices, and good manufacturing practices (GMPs). The groups were later tasked with comparing practices

and preparing guidance on premarket evaluation, PMS/vigilance, quality systems, auditing, and clinical safety/performance.[361]

Governance of the GHTF was introduced with the inauguration of a Steering Committee in 2001[i], whose remit was to establish guiding principles, the roles and responsibilities of its members, and standard operating procedures for the GHTF so that it could adopt a standardised process for developing, agreeing, and finalising guidance documents for publication.[362] According to their guiding principles, GHTF decision-making was by consensus as were the actions taken, which, since their membership consisted of both regulators and industry representatives, meant that industry had significant say in the development and agreement of guidance documents, both in terms of what was developed and what the guidance contained.[363, p.5]

Figure 8.1 was extracted from 'The GHTF Regulatory Model' (GHTF/AHWG-GRM/N1R13:2011).[364] The GHTF Regulatory Model is represented by the yellow boxes, whilst the orange boxes represent the guidance documents produced by the Study Groups. They are reproduced here to show where the focus of regulatory harmonization efforts lay and are illustrated in Table 8.1.

8.1.5. International Medical Devices Regulators Forum (IMDRF)

The GHTF concluded with the founding of the International Medical Device Regulators Forum (IMDRF) as its successor in 2011/2012, which is still in operation today.[365] The IMDRF, unlike the GHTF, is composed solely of regulators, though industry representatives are invited to participate in many of its working groups[ii].[366] The reasons for this change are unclear, but may reflect the political and economic shift away from the free market thinking and neo-liberalism of the 1980s and 1990s towards a stronger state and greater regulatory control[iii].

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[i] Minutes from the GHTF Steering Committee meetings are publicly available in the GHTF archives, however, very few of the minutes from meetings prior to 2001 (either from the GHTF as an overall group or from the original study groups), and I found none for any of the meetings held between its inception and 1997. Nor were any of their guidance documents issued during this period found, though several are available for the latter years, either as archived or current guidance. Thus, it is not possible to gain a clear understanding of how the original guides were developed or what (or who) influenced their contents.

[ii] Industry representatives are excluded from working groups where the exchange of confidential information is required (e.g. adverse event reporting), but it still means that industry is still involved in the development of regulatory guidance. However, it is hard to see how this can be avoided in the very innovative technologies (e.g. artificial intelligence, machine learning, bioprinting of implants, nanotechnology, etc.), because these technologies require cutting edge experts who know what the potential risks may be or what processes require scrutiny.

[iii] Alternatively, it may reflect a recognition that such intimate involvement of the regulated industry with its regulators in designing the rules by which it is regulated represents a significant conflict of interest, which calls the legitimacy of medical device regulation into question and, if realised by the public, may undermine the credibility and trust that the public have in medical device regulation and the medical devices being placed on the market.

Table 8.1. GHTF Guidance documents

Phase & Focus	SG1	SG2	SG3	SG4	SG5
Pre-market	- Definition of a medical device - Risk-based Classification rules - Essential principles of safety & performance - Role of standards - Summary technical file - Pre-market conformity assessment		- Quality Systems for design & manufacture - Process validation - Design control process - Risk management		- Clinical evidence
Placing-on-market	- Labelling - Definition of relevant economic operators	- Adverse event reporting during clinical investigations		- Audit (strategy, reports, & independent verification audits)	
Post-market		- Adverse event reporting guidelines - National Competent Authority Report (NCAR) Exchange Program - Handling of vigilance information - Field safety Corrective Action (FSCA)			

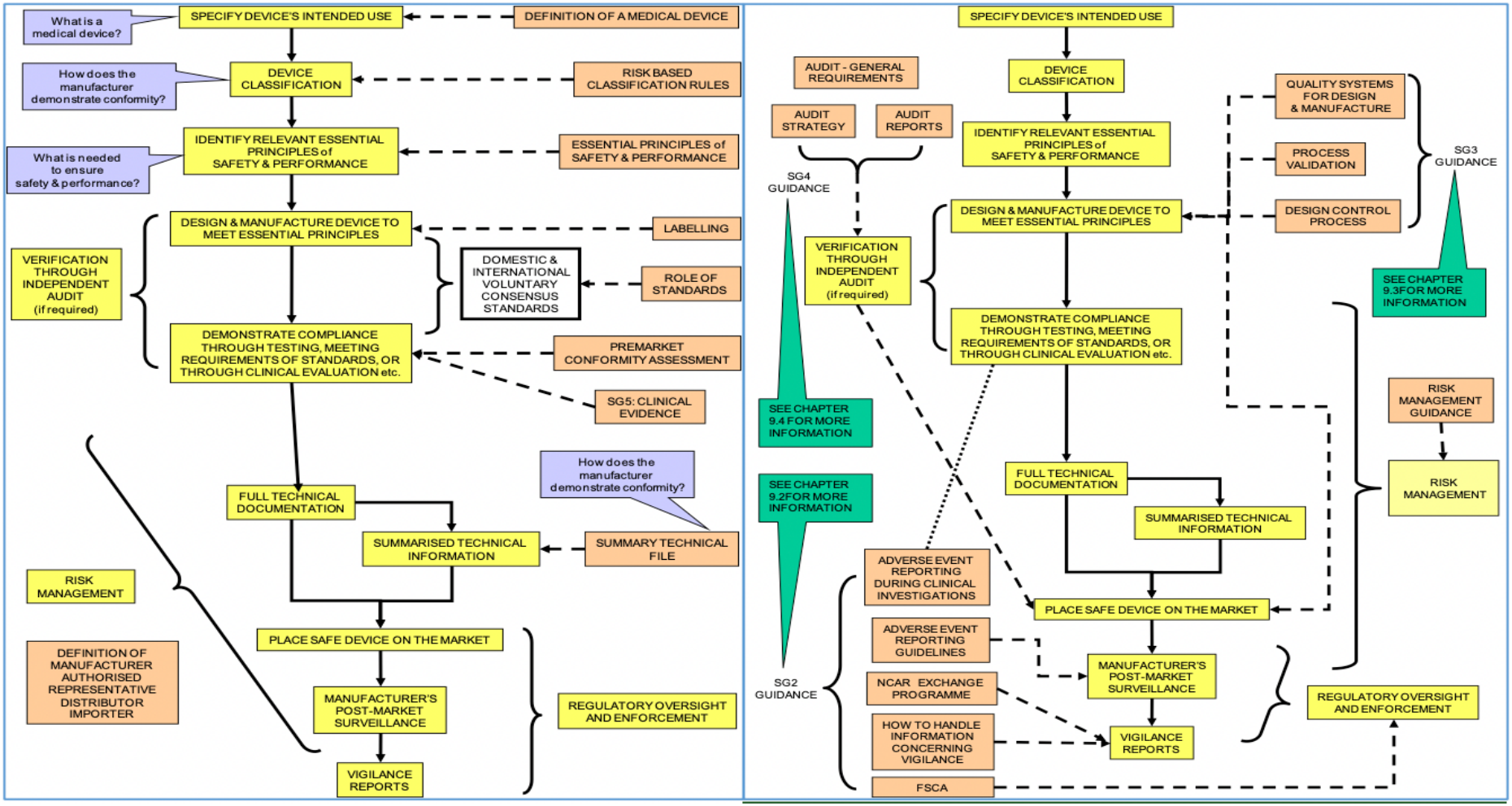

Figure 8.1. The GHTF Regulatory Model, (extract showing guides produced by the Study Groups (SGs) are in orange: SG 1 & 5 on the left, SG 2, 3, & 4 on the right).[363 p.14-15]

The IMDRF's stated mission is to '*strategically accelerate international medical device regulatory convergence to promote an efficient and effective regulatory model for medical devices that is responsive to emerging challenges in the sector while protecting and maximizing public health and safety*.'[367,368] To do this it has a management committee that meets biannually to discuss the IMDRF's programme of work, determine future work, and to approve guidance developed by its working groups.[i369,370] Their current projects are listed in Table 8.2.[370] Guidance issued by the IMDRF takes into account, and is based on, the regulatory processes used by its member organisations, which currently includes the medical device regulators listed in Table 8.3

The IMDRF adopted the most recent final versions of the guidance documents published by the GHTF, beginning its own programme of work by building on this foundation. Some GHTF documents are still in operation as they haven't been changed by the IMDRF.

Figure 8.2 demonstrates the reliance on QMS (Quality Management System), risk management, and the use of design controls (and all of these being documented) to regulate devices in the pre-market phase, with conformity assessment required for placing on the market, and PMS and vigilance in the post-market phase.

There are other international organisations that have influenced the development of the regulation of medical devices in the EU, such as the Global Harmonization Working Party and the Asia Pacific Economic Cooperation's Life Sciences Innovation Forum. However, the organisations described above have had considerable influence over the development of medical device regulation. They illustrate the network of influences that exist at the supranational level and the extent of the pressure to harmonise medical device regulation globally.

[i] Working groups have in the past worked on topics such as the clinical evaluation of medical devices, reviewing the NCAR Exchange Program established by the GHTF (and adopted by the IMDRF), the application of a unique device identifier (UDI), and the development of guidance for particular aspects related to regulating software as a medical device (SaMD).[369]

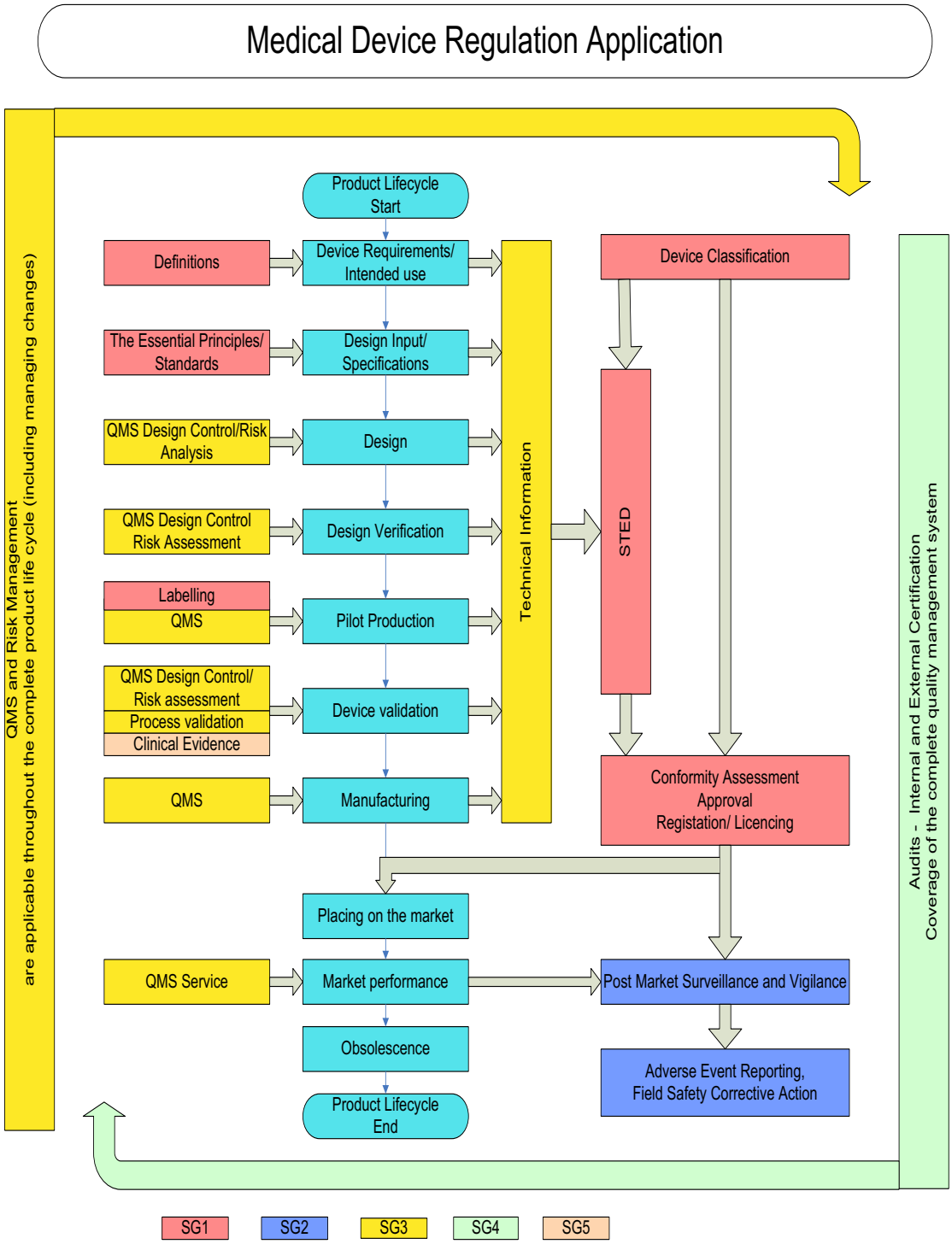

Figure 8.2. GHTF Study Group Work Package.[363, p.16]

Table 8.2. Current IMDRF Working Groups

Current Working Groups	Objectives	Membership
Adverse Event Terminology	Harmonize terminology for reporting adverse events related to medical devices, and further harmonize adverse event reporting datasets to improve signal detection.	Regulators
Artificial Intelligence/Machine Learning-enabled	Seeking to harmonize internationally, principles to help promote the development of safe and effective AI/ML enabled medical devices	Regulators and Industry Stakeholders
Good Regulatory Review Practices	Develop good review practices for pre-market reviews and evaluations.	Regulators
Medical Device Cybersecurity Guide	Manage cybersecurity risks in medical devices through a life-cycle approach. Striking the right balance between pre-market and post-market requirements.	Regulator and stakeholder membership
Personalized Medical Devices (PMD)	Harmonize the regulatory requirements for medical devices that are intended for a particular individual, considering unique characteristics and risks associated with each type of device.	Regulators, Regional Harmonization Initiatives, Official Observers
Quality Management Systems	Ensure alignment of IMDRF QMS and risk management documents with current international standards	Regulators and Industry Stakeholders
Regulated Product Submission	Harmonize the format and content of regulatory submissions.	Regulators
Software as a Medical Device	Promote consistency in regulatory assessment for Software as a Medical Device to reach patients more efficiently.	Regulator and Stakeholder Membership
Extracted from website [Internet]. Accessed 2023 Aug 20. Available from: https://www.imdrf.org/working-groups		

Table 8.3: Members of IMDRF

Nation	Medical Device Regulatory Agency (RA) in 2023	Abbreviated name and Weblink Web link
Australia*	Therapeutic Goods Administration	TGA https://www.tga.gov.au/
Brazil*	Brazilian Health Regulatory Agency	ANVISA https://www.gov.br/anvisa/pt-br/english
Canada**	Health Canada (Medical Devices Directorate)	Health Canada (MDD) https://www.canada.ca/en/health-canada/corporate/about-health-canada/branches-agencies/health-products-food-branch/medical-devices-directorate.html
China*	National Medical Products Administration	NMPA http://english.nmpa.gov.cn/medicaldevices.html
European Union**	European Commission (Directorate-General for Health and Food Safety)	The Commission (DG Santé) https://health.ec.europa.eu/medical-devices-sector_en
Japan**	Pharmaceutical and Medical Devices Agency	PMDA https://www.pmda.go.jp/english/index.html
Russia	Russian Ministry of Health	https://minzdrav.gov.ru/en
Singapore	Health Sciences Authority	HSA https://www.hsa.gov.sg/medical-devices/
South Korea	Ministry of Food and Drug Safety	MFDS https://www.mfds.go.kr/eng/index.do
United Kingdom	Medicines and Health products Regulatory Agency	MHRA https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency https://www.gov.uk/government/publications/report-a-non-compliant-medical-device-enforcement-process
United States of America**	US Food and Drug Administration (Centre for Devices and Regulatory Health)	FDA (CDRH) https://www.fda.gov/medical-devices
Note: One asterisk indicates those nations who were the IMDRF founding members, whilst double asterisks indicates the original founding members of the GHTF. Australia may also be considered a founding member of the GHTF, although it only officially joined the group at its second meeting in November 1993.		

The next subsection describes some of the specific supranational policies that have affected medical device regulation in the EU and globally.

8.1.6. Key policy influences

There are multiple policy arenas, but the regulation of medical devices generally falls within trade policy though it has implications for health. Supranational policy initiatives may take various forms, including specific bilateral or multilateral agreements between nations (such as the GATT), normative pressures (such as international guidelines), and the general push for harmonisation across many spheres of activity, including the regulation of medical devices. Guidelines and standards agreed at an international level increase compatibility between products and provide a greater level of certainty regarding product requirements, which frequently benefits everyone, but they also make it more difficult for alternative approaches or products to emerge or survive. Guidance published by WHO is a significant influencer of national policy, including their guidance on the development of medical device regulation. Two influential regulatory policy guides published by WHO are presented in the next section. Their importance lies in the fact that they endorse a particular approach to medical device regulation, which is based on the previously established regulatory systems, effectively legitimising what previously existed in the more affluent nations and promoting its use globally.

8.1.6.1. Medical device regulations: Global overview and guiding principles

Cheng, in his 2003 guide on medical device regulations prepared on behalf of WHO, asserts that there are three '*critical elements for regulatory attention'*, namely the product, its use, and its representation to users.[97, p.9] He suggests that *'**Pre-market review** contributes to product control, and **post-market surveillance** ensures that medical devices in use continue to be safe and effective*'[i].[97, p.9] He argues that representation of the device to the user in written or verbal form poses a risk to patient safety, and that this should be controlled through labelling requirements, and education of the public and users as a guard against misrepresentation.[97]

Cheng outlines the phases of the life of a medical device that require regulatory control and proposes a common framework for regulating medical devices, along with regulatory tools and some general requirements.[97] The lifecycle phases include the design, manufacture, packaging and labelling, advertisement, sale, use, and disposal of the device.[97] He suggests that the manufacturer is responsible for the pre-market stages (design, manufacture, and packaging and labelling), vendors are responsible for the placing-on-the-market stage activities (advertising and sale of medical devices), and the

[i] However, this assumes that the pre-market review included an assessment and confirmation of their safety and effectiveness in the first place.

users are responsible for the use and disposal of medical devices (post-market stage), as illustrated in Table 8.4. Consequently, different regulatory strategies are needed to control different stages.[97]

Table 8.4. Regulatory framework and controls for medical devices proposed by WHO (adapted from Cheng 2003).[97]

Stage	Control/Monitor	Person (Regulatory Target)	Items or activities regulated
Pre-market	Product	Manufacturer	Device attributes • Safety & performance Manufacturing • Quality Systems Labelling • Accurate description of product • Instructions for use
Placing-on-market	Sale	Vendor	Establishment registration • List products available or in use • Requires vendor to fulfil after-sales obligations Advertising/Representation • Prohibit misleading or fraudulent advertisement
Post-market	After-Sale/Use	Vendor/User	Surveillance/vigilance • After-sale obligations • Monitoring devices' clinical performance • Problem identification & alerts

Cheng recommends that key controls be established in national policy, including basic legislation that puts the requirements on a legal footing, and establishing the necessary regulatory authorities.[97] Suggested key controls include product control, quality system requirements, vendor establishment control, and PMS/vigilance.[97] He advises that product controls should be applied based on their level of risk and, consequently, medical devices should be classified according to risk to enable controls to be applied proportionate to the risk they pose to patients.[97]

Product control

Product controls include instituting a system of pre-market approval (either by local pre-market review or relying on the pre-market review of products by other countries). In the case of relying on pre-market review by other countries, an 'export certificate' verifying

the '*authenticity of regulatory compliance*' should be required, but Cheng warns that export certificates coming from different jurisdictions mean different things, and cautions against relying entirely on these.[97, p.27] Special controls should be added to devices that are intended for home use, are single use, or are refurbished or donated devices. Particularly important are: education of those using home-based devices, and labelling of single-use devices to indicate this[i].[97]

These controls, however, focus on the approval process rather than the desired clinical outcomes from medical devices, the evaluation of which he offers no advice.

Quality system requirements

Cheng defines a '*Quality System'* as the '*organizational structure, responsibilities, procedures, processes and resources needed to implement quality management*' and explains that '*Quality system standards are "generic management standards"*'.[97, p.13] He refers to the international standard developed for quality management systems (QMS) for the design and manufacture of medical devices, namely ISO 13485:1994, and its then pending revision.[ii] He suggests that it is better to use standardised methods for manufacturing as this is good manufacturing practice and reduces the rate of non-conforming products, arguing that '*Prevention has been proven to be more efficient and cost effective in controlling manufacturing processes and maintaining medical device quality*'.[97, p.14] He also points out that this is particularly important for devices where compliance with the regulatory requirements is reliant on a manufacturer's declaration of compliance, which is the case for many devices. Requiring the use of a QMS and auditing its use should, at least in theory, improve the quality of devices produced. He recommends using internationally harmonised standards to achieve this.[97]

This approach is certainly appropriate for improving the quality of devices being placed on the market, however, it assumes that better quality devices are more likely to produce the desired clinical outcomes. It is true that they are likely to be safer, but it does not necessarily follow that they will be clinically effective.

Better quality => more reliable and less likely to fail (therefore safer)
But
High quality =/=> clinically effective & High quality =/=> safe

[i] Alternatively, conducting an assessment of the risks associated with reuse (identifying those that can and those that can't be reprocessed) and putting strict controls in place regarding the reprocessing and sterilisation of those that are potentially reusable if appropriately managed

[ii] Standards are updated regularly, the current version of this one is ISO 13485:2016, which has superseded the 'pending revision' mentioned.

Vendor establishment control

Vendor establishment control means that the government is aware of who is selling devices. Cheng suggests two approaches to achieving this, by requiring notification of sales of medical devices and/or requiring that vendors are registered or licenced to sell devices (establishment licence). Sales notification may be required before or after devices are sold, but places no requirements on who sells them, so this approach is less effective as a mechanism for identifying and contacting vendors in the event of a problem with their devices.

Establishment licencing gives governments more control over who is selling medical devices and increases their ability and power to enforce the legal requirements and after-sales obligations. Governments may also charge a fee from vendors applying for annual renewal of the establishment licence, thereby covering some of the costs of regulation whilst maintaining an up-to-date record of vendors.[97]

Post-market surveillance

Cheng suggests that PMS controls start with the establishment of a national coordinating agency as a '*basic problem-sharing centre'*.[97, p.30] In addition, Cheng recommends preparing a policy or guideline to establish a PMS programme specifically including vendors' after-sales obligations to:

- Register implants
- Maintain distribution records
- Establish a recall procedure
- Mandatory reporting of adverse events
- Establish a complaint handling procedure [97]

In addition to vendor obligations, he recommends that the surveillance by users be promoted using public education, promotion of the surveillance programme, and encouraging regulatory and reporting compliance.[97] All incidents should be investigated to assess the causes, contributory factors, and corrective actions that may be required. He cautions against '*assigning culpability'* as this might discourage reporting.[97, p.30] The standardisation of reporting makes it easier for people to report incidents and for regulators and manufacturers to investigate them, and he advises that '*Governments should adopt recommended formats and procedures*', suggesting those provided by the GHTF.[97, p.31]

It has to be pointed out that these controls, aimed at the product (through a pre-market approval process), the production process (requiring the use of a QMS), the vendor (notification or licencing), and post-market surveillance (via a 'national coordinating

agency'), make no explicit mention of any requirement or methods for assessing the clinical effectiveness of a device. Perhaps it may be assumed that this is part of the pre-market approval process, but this remains an assumption as it is not explicitly expressed. In fact, Cheng argues that it 'i*s easier to measure objectively and quantify performance than clinical effectiveness'*, thereby, justifying focussing on device performance rather than clinical effectiveness.[97, p.4] However, being easier is no justification for not evaluating the impacts that devices have on patients.

WHO has since published additional guidance in the form of a 'Model Regulatory Framework', which, as will be seen has been drawn from this model.

Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices

In 2017, WHO published a Model Regulatory Framework for Medical Devices including in-vitro diagnostic medical devices to address '*the lack of regulatory systems for medical devices in many countries'*, with the aim of supporting nations to establish or improve their medical device regulatory frameworks.[108, p.5] It was developed by international regulators, who acknowledged that much of the model framework is based on documents developed by the GHTF[i] and the IMDRF.

The report recommended that nations take a stepwise approach, similar to that described by Cheng 2003, starting with publishing laws to establish the legal basis for regulation. Then moving on to resourcing a regulatory authority, with increasing attention being paid at a later stage to the enforcement of the laws, and finally moving on to the use of inspection of establishments (i.e. manufacturing plants) and the oversight of clinical trials involving medical devices. To this end, 'The Model' regulatory framework suggests a number of basic level controls that should be instituted first, followed by a set of advanced level controls for sequential implementation.[108] The controls and enforcement mechanisms are broken down into the premarket, placing-on-the-market, and post-market stages (Table 8.5).

Basic level controls include the publishing of law to include the basic level controls and enforcement mechanisms detailed in Table 8.5, with a stepwise increase in regulatory control to result in the advanced level controls detailed in the second half of Table 8.5.

Key features of the premarket basic level controls are that: a definition is established to identify what is a device, and therefore what comes under the scope of any legislation on medical devices; the establishment of a risk-based classification system for devices

[i] The GHTF also has its own Model Regulatory Framework, as described earlier in section 8.4.2.4, but it was published in 2011, after Cheng's model.

Table 8.5: Basic and advanced regulatory controls and enforcement mechanisms, adapted from Figure A4.4 of WHO's Model Regulatory Framework.[108]

Publish law including these basic level controls and enforcement mechanisms:		
Premarket	**Placing-on-the-market**	**Post-market**
Definition of a medical device	Registration of establishments	Vigilance reporting system
Device classification system	Listing of medical devices	Mandatory notification of field safety corrective actions (FSCAs) by manufacturers
'Essential Principles' for safety and performance	Importation controls	Withdrawal procedure for unsafe medical devices
Basis for 'reliance and recognition'[i]		Procedure to warn users of safety alerts
Requirements for conformity assessment		Conduct market surveillance
Require manufacturers to have a QMS		
Labels and labelling requirements		
False, deceptive, or misleading advertising should be prohibited		
Provide mechanism for exceptional pre-market circumstances		
Advanced level controls and enforcement mechanisms		
Premarket	**Placing-on-the-market**	**Post-market**
Create oversight of clinical investigations	Conduct in-country QMS audits	Establish a PMS and vigilance reporting system within the regulatory authority
Appoint and have oversight of a conformity assessment body (CAB)	Review applications for market authorisation compliance with Essential Principles	Require mandatory reporting of adverse events by manufacturers
Recognise standards		Inspect registered establishments
Adopt a medical device nomenclature system		Provide testing laboratory(ies)
Control advertising and promotion		

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[i] Reliance and recognition refers to the process where a national regulatory authority has a mechanism for recognizing the regulatory requirements from another jurisdiction as meeting domestic requirements and, thereby, allowing medical devices to enter the domestic market on the basis of meeting those requirements.

to enable regulatory controls to be applied proportionate to the level of risk; establishment of essential principles[i] of safety and performance which medical devices and their manufacturers must comply with, and against which they will be assessed for compliance; and the establishment of conformity assessment procedures to assess compliance. Since the 'Essential Principles' for safety and performance are key to their recommendations for the regulation of medical devices that section of the text is reproduced here in its entirety in Box 8.3. These essential principles don't differ substantively from those produced by the GHTF/IMDRF, or those required by the MDD, except in the level of detail.

The general Essential Principles apply to all medical devices and are supplemented by those principles specific to particular medical device types (e.g. implants or electrically powered devices).
The general Essential Principles of safety and performance for medical devices include the following.

- *The processes for the design and production should ensure that a medical device when used according to the intended purpose and meeting the conditions of technical knowledge and training of the user is safe and does not compromise the clinical condition of the patient or the health of the user.*
- *The manufacturer should perform a risk assessment to identify known and foreseeable risks and to mitigate these risks in the design, production and use of the medical device.*
- *Medical devices should perform as the manufacturer intended when used under normal conditions.*
- *Performance and safety should not be affected during the lifetime of a medical device in such a way that it affects the safety of the patient or the user.*
- *Performance and safety should not be affected by transport or packaging and storage, provided the instructions for packaging, transport and storage are followed.*
- *Known and foreseeable risks should be weighed against the benefits of the intended purpose.*

Ensuring that a medical device conforms to all relevant Essential Principles is the responsibility of the manufacturer. However, the manufacturer's evidence of conformity, recorded in its technical documentation, may be subject to review by the regulatory authority, either before or after market introduction. The medical device regulation shall specify the extent of the regulatory authority's involvement with different classes of device. While retaining responsibility for the decisions it makes, the regulatory authority may appoint one or more conformity assessment bodies (CABs)[5] to assist it in this task (see section 4).[108]

Box 8.2: Essential Principles, extracted from the Model Regulatory Framework[108]

The Model suggests that assessment of compliance with the essential principles generally involve the conformity assessment of three aspects:

[i] These 'essential principles' actually mean minimum requirements and are not to be confused with Eccleston's principles of regulation, which focus on ensuring the safety and effectiveness of devices. These minimum requirements are more technical in nature than clinical.

- the quality management system (QMS);
- the technical documentation;
- and the declaration of conformity.[108, p.12]

Quality management systems are not generally audited for low risk devices apart from those aspects of quality management related to the sterilizing process or the accuracy of the measuring function of a low risk device. For higher risk devices the Model suggests that the '*regulatory authority should have confidence that current and appropriate QMS is in place or otherwise conduct a QMS audit prior to marketing authorization'*.[108, p.12] Submission of technical documentation is not generally required for the lowest risk class devices, and though it may be requested for medium risk devices it is not normally reviewed. As for high risk or the highest risk devices, the Model recommends that the regulatory authority should undertake a review of sufficient depth to determine conformity of the design and manufacturing processes with the essential principles of safety prior to the device being allowed to be placed on the market. Although, a declaration of conformity (DoC) must be made by manufacturers for all classes of device, this is not generally requested by the regulatory authorities for low risk devices. However, the Model recommends that the DoC be submitted for all higher risk devices to the regulatory authority for review and verification of compliance with the requirements.

As can be seen from the proposed controls presented above the Model, WHO supports a system of pre-market assessment of regulatory compliance and PMS of AMDEs, with inspection of premises that relies on external assessment bodies.[i] These processes are facilitated by the definition of essential principles (i.e. minimum requirements), the use of recognised standards, and the deployment of systems to manage the quality of the design and production processes and the risks associated with the resultant devices It relies on documentation to declare, assess, and confirm that the minimum requirements have been met, and a PMS is in place to detect unsafe devices. This is a very similar to the approach taken in the EU's regulatory framework.

8.2. State Intervention

There are two legal frameworks currently in place for medical devices in the EU as the transition period between the original EU legal framework and the revised one continues to take place.[ii] This research explores both legal frameworks, focussing primarily on the

[i] It should be noted that there is an absence of a requirement for evidence of clinical effectiveness/safety.
[ii] It had been intended that the transition would be completed by 2024, but it was extended to 30th December 2028, partly due to Covid-19, but also partly due to the necessary structures/systems not yet being in place for the full implementation of the revised framework.

original legal framework and the issues with it, as the revised framework was supposed to address these, but it was itself influenced by the regulatory history resulting in the MDD.

The original legal framework for medical devices in the EU was/is based around a set of three medical device directives (MDDs) enacted in the 1990s,[1,4,5] supplemented with implementing and amending legislation.[5,371–374] Directives are not directly applicable to the laws of Member States (MS), so each MS must transpose EU directives into national law. This introduces variability in the interpretation and implementation of the directives, as national laws differ across MS. There are multiple reasons why the MDDs were in need of revision, but one of the driving forces was the widely publicised failure of a number of devices, namely the Poly Implant Prothèse (PIP), the metal-on-metal (MOM) hip, and more recently, urogenital surgical meshes.[14,15,152,375] These failures called the integrity of the regulatory process into question and caused the public and healthcare professionals to lose confidence in its ability to guarantee adequate patient safety.[17,18,376]

The revised legal framework, which was enacted in 2017, consists of two medical device regulations (the MDR and the IVDR),[2,3] supplemented by amending and implementing legislation.[377,378] In contrast to EU directives, EU regulations are directly applicable to MS law, therefore, the MDRs are subject to less variability in their interpretation and implementation across MS.

These legal frameworks are the subject of Chapter 9, but to understand them it is first necessary to understand who the regulators were and the policy context within which they were enacted.

At the EU level, the 'rule-makers' are the legislative, executive, and judiciary institutions of the EU and its precursors. Section 8.2.1 introduces the EU regulatory institutions and, since institutions and laws are not static, three sub-sections describe the legal history of the institutions (Section 8.2.1), their composition at the time of the MDD (Section 8.2.1.2), and their composition at the time of the MDR (Section 8.2.1.3), followed by a discussion on these in Section 8.2.1.4.

8.2.1. The regulatory institutions – 'Rule-makers'

8.2.1.1. Treaties establishing the institutions

The European Economic Community (EEC) was established in 1957 by six nations signing the Treaty of Rome (Belgium, France, West Germany, Italy, Luxembourg, and the Netherlands). It was modelled on the Treaty of Paris establishing the European Coal and Steel Community (ECSC), signed by the same nations to enable a sharing of coal and steel resources to rebuild up their economies after the second world war.

By signing these treaties, the signatory member states (MS) essentially transferred their national power to control the marketplace and empowered the governing institutions of the communities established by the treaties, this allowed the EEC to enact legislation controlling the rules applied by the MS to products entering their markets. Power transferred across the institutions also, as the institutional structures and the rules governing the legal procedures they were bound to follow to enact legislation were repeatedly amended, rebalancing the power between the MS and the EEC and between the regulatory institutions.

Following the enactment of the Treaty of Rome, and subsequent Single European Act (SEA), the EEC was legally bound to try to achieve the objectives set out for it in the Treaty of Rome. The main goal of these and subsequent treaties, shown in Table 8.6, was to create an internal market, removing barriers to trade, and enabling free movement of goods. Health was not a goal of these treaties and healthcare remained the responsibility of the MS. Hence, the legislative acts enacted by the EEC, or its successors the European Community (EC) and the EU, were not patient-centred and did not attend to the clinical effectiveness of medical devices. The key features of the treaties are summarised in Table 8.7.

The institutions involved in enacting the EEC's medical device legal framework were the Commission (representing the interests of the EEC), the Council (representing the governments of the MS), the European Parliament (EP, originally called the Assembly,[379] Article 7 it represents the people), and the Economic and Social Committee (ESC, representing employers, workers, and 'various interests')[380, p.66]

The working groups (WGs) for each of these EEC institutions involved in enacting the MDD, (the Commission drafting the proposal, the European Parliament (EP) providing oversight and feedback to ensure the EEC didn't overstep its legal remit, the Economic and Social Committee (ESC), and the Council enacting the final directive) were each those representing industry rather than health. This changed with the enactment of the MDR, reflecting the concerns that people had about medical devices, yet industry still had a significant input, as evidenced by the fact that the Directorate General (DG) of the Commission representing health drafted the proposal, starting the legislative procedure, yet it was the DG representing industry who drafted the final version of the MDR. Table 8.8 summarises the WGs involved in enacting the MDD and MDR.

Table 8.6. Stated goals of the major European treaties establishing the EEC/EU

Treaty	Stated goals
The Treaty of Paris (1951)	The mission of the European Coal and Steel Community is to **contribute to economic expansion**, the **development of employment** and the improvement of the **standard of living** in the participating countries **through the institution**, in harmony with the general economy of the member States, of **a common market** as defined in Article 4. The Community must progressively establish conditions which will in themselves assure the **most rational distribution of production** at the **highest possible level of productivity**, while **safeguarding** the continuity of **employment** and avoiding the creation of fundamental and persistent disturbances in the economies of the member States. (Article 2)
The Treaty of Rome (1957)	It shall be the aim of the Community, **by establishing a Common Market** and **progressively approximating the economic policies** of Member States**, to promote** throughout the Community a **harmonious development of economic activities**, a continuous and balanced **expansion**, an increased **stability**, an accelerated **raising of the standard of living** and **closer relations** between its Member States. (Article 2)
Single European Act (1987)[379,381]	The European Communities and European Political Co-operation shall have as their **objective** to contribute together to making concrete progress towards **European unity**. The European Communities shall be founded on the Treaties establishing the European Coal and Steel Community, the European Economic Community, the European Atomic Energy Community and on the subsequent Treaties and Acts modifying or supplementing them. (Article 1, 1st & 2nd para.s)
The Treaty of Maastricht (1992)	Article B The Union shall set itself the following **objectives**: — to **promote economic and social progress** which is balanced and sustainable, in **particular through the creation of an area without internal frontiers**, through the strengthening of **economic and social cohesion** and through the establishment of **economic and monetary union**, ultimately including a single currency in accordance with the provisions of this Treaty ; — to assert its identity on the international scene, in particular through the implementation of a common foreign and security policy including the eventual framing of a common defence policy, which might in time lead to a common defence; — to strengthen the protection of the rights and interests of the nationals of its Member States through the introduction of a citizenship of the Union ; — to develop close cooperation on justice and home affairs ; — to maintain in full the 'acquis communautaire' and build on it with a view to considering, through the procedure referred to in Article N(2), to what extent the policies and forms of cooperation introduced by this Treaty may need to be revised with the aim of ensuring the effectiveness of the mechanisms and the institutions of the Community. The objectives of the Union shall be achieved as provided in this Treaty and in accordance with the conditions and the timetable set out therein while respecting the principle of subsidiarity as defined in Article 3b of the Treaty establishing the European Community.

The Treaty of Lisbon (2007)[382]	'Article 2 1. The Union's aim is to **promote peace**, **its values** and the **wellbeing of its peoples**. 2. The Union shall offer its citizens an area of freedom, security and justice without internal frontiers, in which the free movement of persons is ensured in conjunction with appropriate measures with respect to external border controls, asylum, immigration and the prevention and combating of crime. 3. The Union **shall establish an internal market**. It shall work for the **sustainable development** of Europe **based on** balanced **economic growth** and **price stability**, a highly **competitive social market** economy, **aiming at full employment and social progress**, and a **high level of protection and improvement of the quality of the environment**. It shall promote scientific and technological advance. It shall combat social exclusion and discrimination, and shall promote social justice and protection, equality between women and men, solidarity between generations and protection of the rights of the child. It shall promote economic, social and territorial cohesion, and solidarity among Member States. It shall respect its rich cultural and linguistic diversity, and shall ensure that Europe's cultural heritage is safeguarded and enhanced. 4. The Union shall establish an economic and monetary union whose currency is the euro. 5. In its relations with the wider world, the Union shall uphold and promote its values and interests and contribute to the protection of its citizens. It shall contribute to peace, security, the sustainable development of the Earth, solidarity and mutual respect among peoples, free and fair trade, eradication of poverty and the protection of human rights, in particular the rights of the child, as well as to the strict observance and the development of international law, including respect for the principles of the United Nations Charter. 6. The Union shall l pursue its objectives by appropriate means co m mensurate with the competences which are conferred upon it in the Treaties.'
Note: **Bold** *added for emphasis*	

Table 8.7. Key features of the main treaties establishing the EEC/EU

Date	Treaty	Key features
April 1951	*The Treaty of Paris*	• Established the European Coal and Steel Community • Six member states: France, Germany, Belgium, Italy, Luxembourg, and the Netherlands • Goal of economic recovery and economic development post-WWII • Established a set of governance institutions - the High Authority (predecessor of the European Commission), the Special Council of Ministers (predecessor to the Council of the EU), the Joint Assembly (predecessor to the European Parliament), and the Court of Justice, (predecessor to the European Court of Justice).
March 1957	*The Treaty of Rome*	• Established the European Economic Community (EEC) • Introduced the customs union and a common trade policy for MS • Set out the number of seats assigned to each MS for each institution, ensuring that the bigger countries had more representatives, and therefore, voting power proportionate to their population size.
1972-1985	*Accession treaties*	• Expanded EEC membership to Denmark, Ireland, the UK, Greece, Spain, and Portugal • Expanded the common market for goods to twelve countries
1992	*The Treaty of Maastricht*	• Formally created the EU • Extended the remit of the EU to a common foreign and security policy and MS cooperation on justice and home affairs • Introduced the co-decision procedure, entailing two readings of draft legislation in Parliament, and gave the EP greater say in the decision-making process • Established the European Central Bank, increasing EU influence over MS monetary and fiscal policy
1995-2001	*Accession treaties*	• Expanded EEC membership to Austria, Finland, and Sweden • Increased the use of QMV in more policy areas
2007	*The Treaty of Lisbon* [382]	• Further extended the power of the EU over more policy areas • Increased the power of the EP to cover 73 areas of policy-making and to accept/reject international agreements • Introduced the special legislative procedure and the concept of non-legislative acts which are not subject to the same level of scrutiny or transparency

8.2.1.2. Regulatory institutions at the time of the MDD

The treaties and their respective timelines, prior to enacting the MDD, and afterwards, up until the MDR was enacted, are illustrated in Figures 8.3-8.4. The result of these treaties was that there was a common market for goods (and for certain services) between twelve nations that allowed raw materials and finished products to be traded between them without customs or tariffs. However, there were still obstacles to trade that created 'technical' barriers to the free movement of goods, people, services, and capital, which the EEC tried to address using what came to be called the 'New Approach'.[383] This was facilitated by an intergovernmental conference held in 1985, resulting in the Single European Act, signed on 28th February 1986.[381] The Single European Act changes that led to the enactment of the MDD.

The regulators were the governing institutions of the EEC as they were composed by the treaties in force at the time of enacting the MDD[i]. Table 8.9 summarises the key characteristics of these institutions at the time of the MDD.

Table 8.8. Sector represented by the Institutions' working groups enacting the MDD/MDR

	MDD lead working group	**MDR lead working group**
Commission	DG III – Industry	DG- SANTE Directorate-General for Health and Consumers; later the lead became the Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs (DG-GROW)∞
European Parliament	Committee on Economic and Monetary Affairs and Industrial Policy (ECON)†	Committee on the Environment, Public Health and Food Safety (ENVI)∞
Council	Not identified.	Employment, Social Policy, Health and Consumer Affairs Council configuration (EPSCO)∞ (see ST-9769-2015-INIT)
ESC	Section for Industry, Commerce, Crafts and Services§ (see CELEX 51992AC0086 EN TXT, p.1)	Section for the Single Market, Production and Consumption∞ (see OJ C 2013 133 FULL EN TXT, p.52)
†*https://eur-lex.europa.eu/legal-content/EN/HIS/?uri=CELEX:31993L0042&qid=1712785090584#121926* ∞ *https://eur-lex.europa.eu/legal-content/EN/HIS/?uri=CELEX:32017R0745*		

[i] The Treaty of Rome as amended by the SEA and the accession treaties admitting the UK, Denmark, Ireland, Greece, Spain, and Portugal.

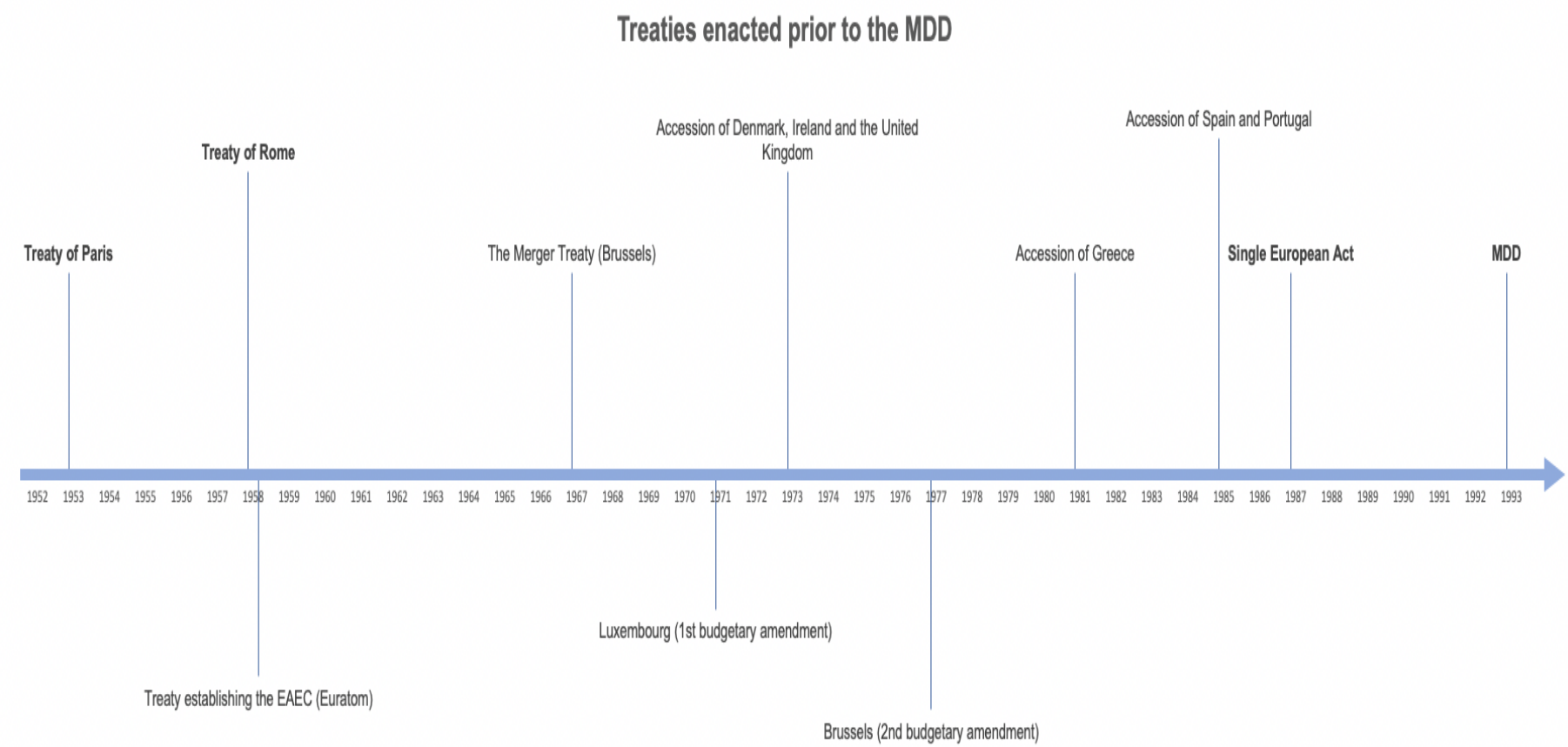

Figure 8.3. Timeline of treaties enacted and entered into force prior to the MDD

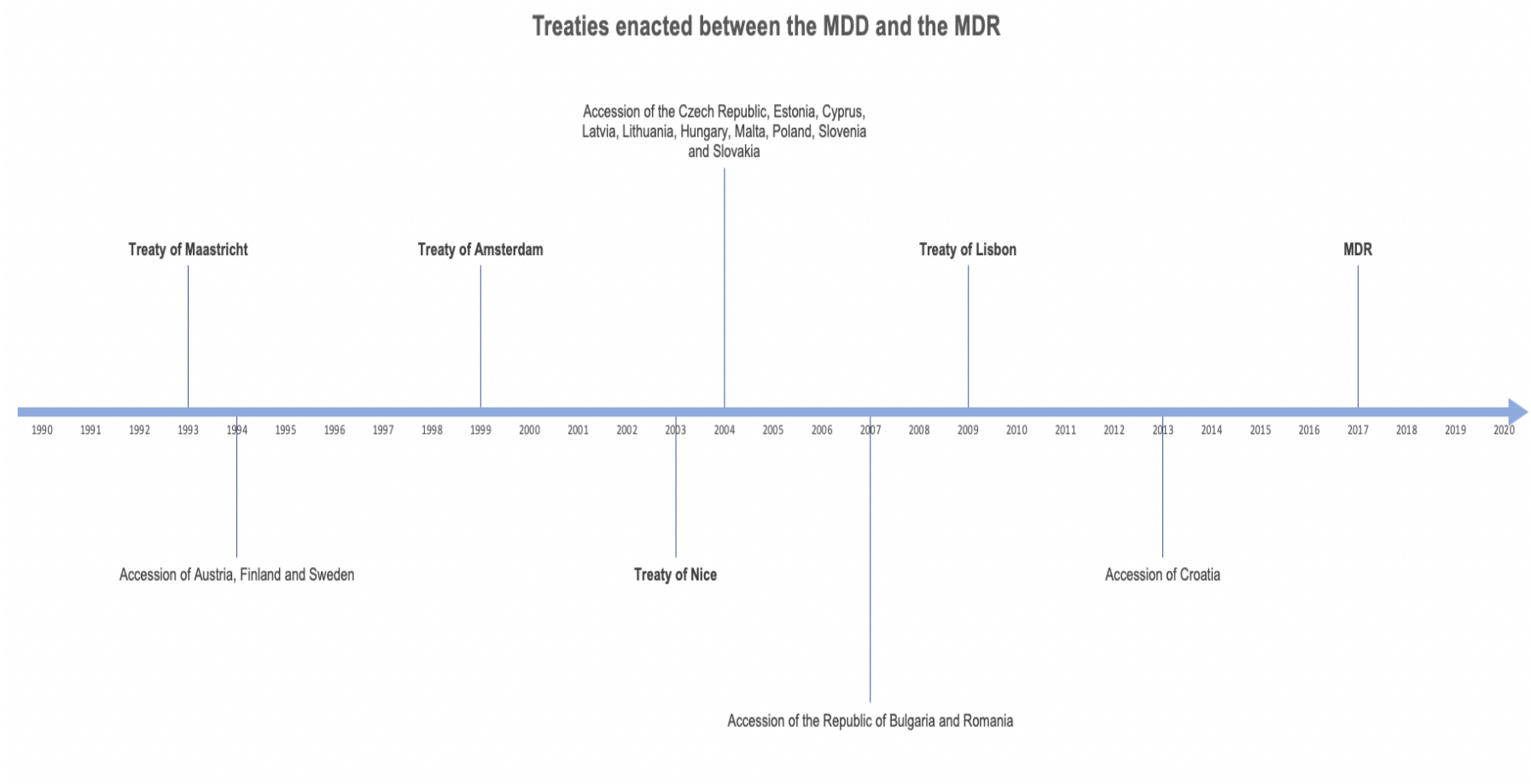

Figure 8.4. Timeline of later treaties in force prior to the MDR

Table 8.9. Institutions of the EEC and their composition at the time of the MDD

Institutions	**European Parliament**	**The Council**	**The Commission**	**Court of Justice**	**Economic & Social Committee**
Treaty of Rome as amended , OJ C 224, 31.8.92; Articles:	137-144	145-154	155-163	164-188	193-198
Role/ Responsibility	shall exercise the powers conferred upon it by the Treaty	ensure coordination of the general economic policies of the MS; have power to take decisions; confer power on the Commission to implement the acts adopted by Council (may also take on implementing powers itself)	to ensure the proper functioning and development of the common market: it shall: ensure application of the Treaty (& acts of its institutions); make recommendations, give opinions on matters relevant to the Treaty; have power of decision and shape measures to be taken by the Council & EP; have power to implement acts of the Council.	shall ensure that in the interpretation and application of this Treaty the law is observed	Advisory
Representing	The people	MS Governments	The European Union	Independent	Independent, but represent the economic groupings & the public

Membership	518[i]	12[ii]	17[iii]	13[iv]	189[v]
Election/ Selection	'direct universal suffrage' representing the people	Representative Minister nominated from each MS	Governments, after consulting the nominated President, nominate the other members; entire group approved by EP; appointed by Governments by common accord.	Chosen if their 'independence is beyond doubt' from amongst highest qualified judges in MS. Appointed by MS Governments by common accord.	Representatives of the various categories of economic and social activity, (particularly, representatives of producers, farmers, carriers, workers, dealers, craftsmen, professional occupations and of the general public) appointed by the Council by UV.
President	Elected by EP from amongst its members	6 month rotating presidency between MS	Governments, after consulting EP, nominate President (by common accord) & appointed at the same time as the other members.	Elected by ECJ Judges from amongst themselves, 3 year term, renewable	Chair & officers elected by ESC, 2 year term

[i]Seats apportioned: 81– UK, IT, FR, DE; 60 – ES; 25 – NE; 24 – BE, EL, PT; 16 – DK; 15 – IE; 6 – LU, Article 10 of the Accession Treaty admitting Spain and Portugal, amending Article 2 of the EEC Treaty.
[ii] For QMV, the weights are: 10 – DE, FR, IT, UK; 8 – ES; 5 – BE, EL, NE, PT; 3 – DK, IE; 2 – LU, Article 14 of the Accession Treaty admitting Spain and Portugal, amending Article 148(2) of the EEC Treaty.
[iii] Article 15 of the Accession Treaty admitting Spain and Portugal, , amending Article 10(1) of the Treaty establishing a single Council and a single Commission of the European Communities.
[iv] Article 17 of the Accession Treaty admitting Spain and Portugal, amending Article 165 of the EEC Treaty.
[v] Seats apportioned: 24 – DE, FR, IT, UK; 21 – ES; 12 – BE, EL, NE, PT; 9 – DK, IE; 6 – LU, Article 21 of the Accession Treaty admitting Spain and Portugal, amending Article 194 of the EEC Treaty.

Term of Office	Not specified in the treaties	Not specified in the treaties	4 years, renewable (increased to 5 by the Maastricht Treaty)	6 years, partial replacement every 3 years (6 or 7 alternately). Retiring judges & AGs are eligible for reappointment.	4 years, renewable
Act by	AMV[i] (unless specified otherwise)[Art 141]	Majority of its members (except where otherwise specified) [Art 148]	Majority of its members (except where otherwise specified)[Art 163]	Makes judgements	ESC adopts its rules of procedure. It may issue an opinion when consulted by the Council or the Commission, or on its own initiative where it considers it appropriate.
Structure	Political party structure The work of drafting opinions is done by Parliamentary committees (structured to reflect the political composition of the European Parliament) along specific	Presidency rotates between MS every 6 months. Council meets in different configurations. A committee of Permanent Representatives of the MS prepares the work of the Council's and carries out the tasks assigned to it by the Council [Art 151]	President & 6 Vice-Presidents[ii], 2 year term, renewable. The Commission is organised into Directorates (Directorates-General, DGs) responsible for specific policy areas (listed in Table 8.x)	Registrar of ECJ appointed by ECJ; Court of First Instance	Specialized sections for the 'principal fields of the Treaty', including an agricultural & a transport section. Sections cannot be consulted independently of the ESC. Sub-committees may be established to prepare on specific questions or fields or

[i] AMV indicates absolute majority vote, which means that a majority of the votes cast is required for an institution to act.
[ii] Article 16 of the Accession Treaty admitting Spain and Portugal, amending Article 14 of the Treaty establishing a single Council and a single Commission of the European Communities.

	policymaking areas. See Table 8.x				to draft opinions for ESC to consider.
Meeting	Annual – 2nd Tues in March[i]; Extraordinary session on request by a majority of its members or if requested by the Council or Commission	When convened by its President (own initiative) or on request by a Council member or the Commission	Decisions made at meetings only valid if the quorum set in its rules of procedure are present	Sits in plenary (all judges) or in chambers (3-4 judges, for preparatory cases or adjudicating in certain categories of case). Full ECJ when MS or community institution is party to the case	Meet on request from the Council or the Commission, or on its own initiative, convened by chairman.
Assisted by	Not specified	General Secretariat (appointment of the Secretary-General by UV[ii])	Economic & Social Committee (ESC); 'Standing Committees' whose role is to assist with implementing acts, whilst ensuring the Commission doesn't overstep its legal remit regarding these.	6 Advocates-General x 6 years, partial replacement every 3 years	Not specified

[i] This was originally the third Tuesday in October in the Treaty of Rome, but was amended by the Merger Treaty (Treaty establishing a single Council and a single Commission of the European Communities), 11965F, Article 27. It follows the day set for the annual meeting of the Assembly for the ECSC, 11951K, Article 22.
[ii] UV indicates the requirement for unanimity (i.e. unanimous vote) before an institution may act.

8.2.1.3. The European Union's institutional structures at the time of the MDR

The institutional structures had changed little at the time that the MDR was enacted, but their composition had expanded to accommodate the twenty-eight MS. The European Parliament had expanded to 751 members, the Commission and the Council had 28 seats each, whilst the ESC and the CoR each had 350-353 members (with the same number of alternates for the CoR). The number of working groups and committees in each institution have also grown. This greatly increased size in the EU and its institutions reflected not only its increased power, but also the fact that decision-making was more complex and therefore slower, with legislative debates and procedures taking longer to conclude.

The Commission and the Council were also obliged to consult the ESC for acts that impacted civil society or required changes in the legislation of MS, and the CoR for acts with a regional or cross-border impact. The other institutions of the EU have much the same roles as previously, though more power has been transferred to the EP.

8.3. EEC/EU regulatory policy

The regulatory institutions are required to follow specified procedures when meeting, preparing opinions and recommendations, or enacting legislation. However, these procedures also changed over time. The Cooperation Procedure was the applicable procedure through which the original medical device legal framework was introduced, and it prepared the ground for co-decision, renamed the ordinary legislative procedure, which was the procedure used later for revising the medical device legal framework.

In this section, 8.4, I describe the procedures that the EEC was required to follow at the time the MDD was enacted, and to a lesser extent, at the time the MDR was enacted.

8.3.1. The Cooperation Procedure

The cooperation procedure was introduced in 1987 by Article 6 of the SEA amending Article 149 of the Treaty of Rome.'[379, Article 6(1)] This procedure involved two readings of a proposed piece of legislation in Parliament, where there had only been one before, thereby, increasing the powers of the EP to influence the contents of legislation. However, the Council remained the sole legislator. The policy areas that were subject to the cooperation procedure were mostly those relating to the removal of technical barriers impacting the freedom of movement of goods, services, capital, or businesses.[379, Article 6(1)]

8.3.1.1. Proposal

A proposal must first be prepared by the Commission and submitted to the Council. The Council could amend it (with a unanimous vote) or approve it on the basis of a qualified majority, but It had to seek the opinion of the EP before it submitted its position on the draft. Following consideration of Parliament's opinion, the Council adopted its common position, and communicated this to the EP, explaining why it had adopted this common position. The Commission also had to explain its position to Parliament.

8.3.1.2. Common position

Parliament could approve, propose amendments (based on an absolute majority of its component members, i.e. 260 of 518 votes), or unanimously reject the Council's common position within three months of receiving it. If it reached or communicated a decision within three months (with one additional month, if agreed with the Council) the act was adopted with the text of the common position. If the EP rejected the common position or it proposed amendments, the Commission had to re-examine the common position within a month and consider Parliament's proposed amendments, preparing a re-examined proposal.

8.3.1.3. Re-examined Proposal

This re-examined proposal, and any amendments which it had not accepted, along with the Commission's opinion on them, were sent to the Council. The Council could, within three months (plus one additional month, if agreed with the EP), adopt the re-examined proposal on the basis of a QMV, or amend it on the basis of unanimity. It could also adopt, based on a unanimous vote (UV), the amendments that were not accepted by the Commission. If the Council didn't reach a decision within the timeframe, then the Commission's proposal was '*deemed not to have been adopted'*.[379, Article 7] The Commission could alter its proposal at any stage in the process, if the Council had not yet acted (i.e. enacted legislation).

The Cooperation Procedure is summarised in Figure 8.5, showing the different options available to the institutions. It is notable that to reject a proposal required UV, whilst to adopt required a QMV, making it easier to adopt than to reject.

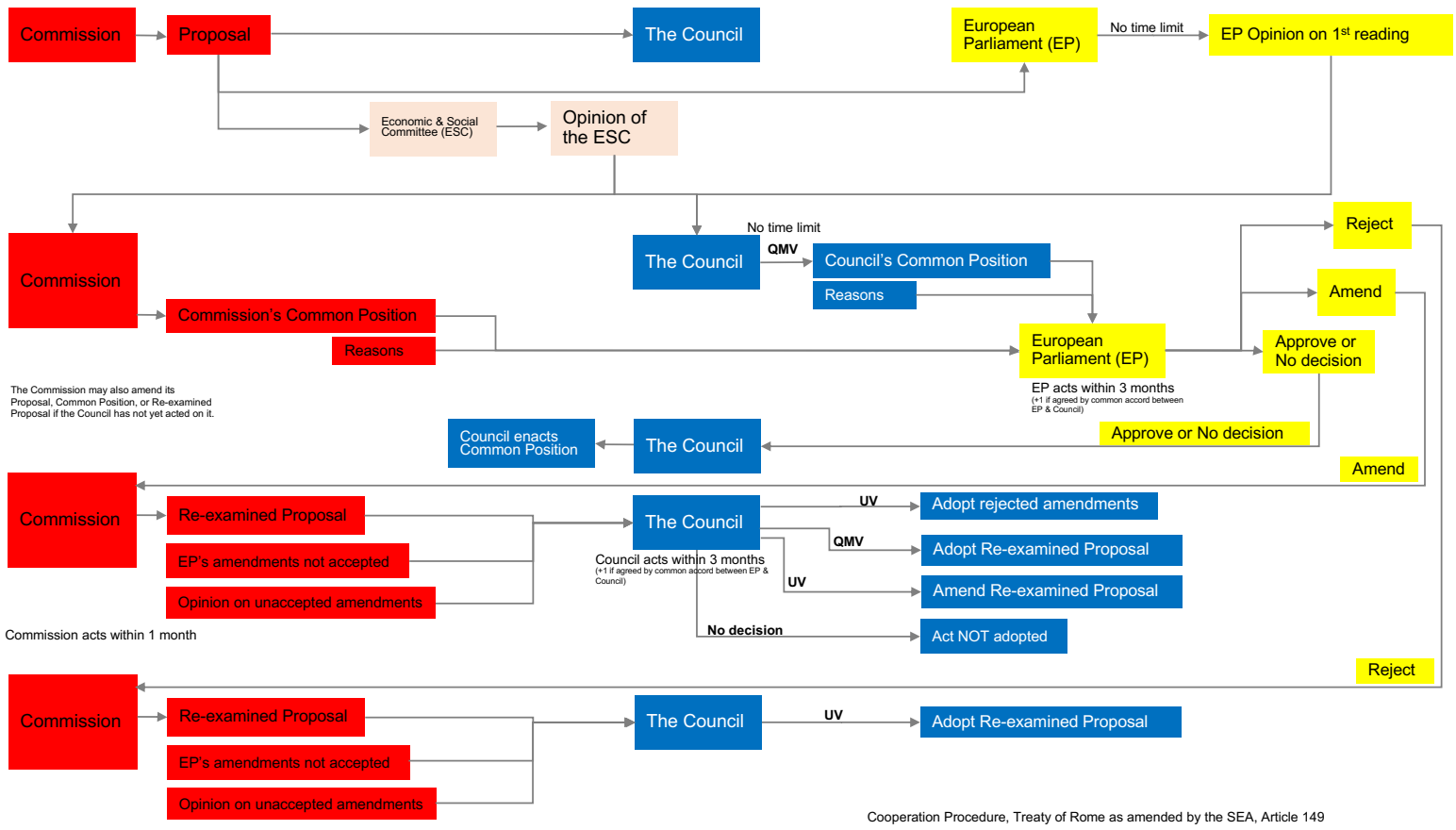

Figure 8.5. The Cooperation Procedure

8.3.2. Enacting the Medical Device Directive

8.3.2.1. Proposal

The proposal for a council directive concerning medical devices was developed by DG III – Industry[i], which meant that its primary focus was on promoting industrial growth. It was adopted by the Commission on 25 July 1991, and the document (dated 23 August 1991) was transmitted to Council (30 August 1991) and to the EP (11 September 1991).

8.3.2.2. ESC opinion

The ESC was consulted. It published its opinion in the Official Journal of the Economic Communities on the 30th of March 1992. It stated that '*The Section for Industry, Commerce, Crafts and Services, which was responsible for preparing the Committee's work on the subject, adopted its Opinion on 8 January 1992. The Rapporteur was Mr Flum.*'[384] Amongst the comments in the ESC's opinion it states that '*The Committee also notes that no ethical principles can or should be laid down by this directive'*,[384, 1.4] thus highlighting the lack of consideration of the ethical dimension of introducing devices to the market intended for medical care.

The ESC opinion also suggests that national standards might be lowered by the proposed directive:

'*Article 5(1) diverges textually from Article 5 of Directive 90/385/EEC which has a similar content. It is not clear whether it is intended to lower relevant national standards thereby. Clarification is requested on why textual differences are regarded by the Commission as being necessary here.*'[384, 2.3.1]

The ESC also called for the central recording and evaluation of potential harms due to medical devices to be extended to all possible harms (and not just the most severe ones), to include Class I devices, and that national health insurance bodies (i.e. funders of healthcare) be informed '*so that claims for damages could be made where appropriate'.* [384, 2.7.1-3] This recommendation was not acted on by the Council.

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[i] This means that with Industry as the lead DG, the key inputs into the proposal were from industry. According to the procedure records the associated services were DG XXIII – Enterprise Policy, Distributive Trades, Tourism and Cooperatives; DG I – External Relations: Commercial Policy and Relations with North America, the Far East, Australia and New Zealand; Directorate-General for Budget; Directorate-General for Employment, Social Affairs and Inclusion; Secretariat-General; Directorate-General for Human Resources and Security; Directorate-General for Health and Consumers; Directorate-General for Environment; Directorate-General for the Information Society and Media; Directorate-General for Research and Innovation; Directorate-General for Financial Control. Thus, the DG responsible for healthcare was also involved, but as it was not the lead it had less influence, particularly as so many other services were involved.

8.3.2.3. Opinion of the European Parliament

The European Parliament assigned the proposal to the Committee on Economic and Monetary Affairs (ECON), with Pierre Lataillade as the rapporteur. The opinion of the Committee on the Environment, Public Health and Food Safety (ENVI)[i] was also sought (issued on 26 February 1992). ECON submitted its report to the Parliament on 15 April 1992[ii]. This meant that the proposal was evaluated by the Parliament primarily through an economic lens, with the health perspective taking a subsidiary role. This is evidenced further by the fact that just seven weeks elapsed between when ENVI issued its opinion to when ECON submitted its overall report to Parliament. The Parliament's first position reading (approval with amendments) was published on 13 May 1992, as well as the Commission's position on Parliament's amendments on first reading as 'Partial agreement'.

8.3.2.4. Amended Proposal

Towards the end of September, the Commission published its amended proposal, and transmitted it to the Council and to the Parliament. Council reached an agreement on a common position mid-December, placing it on the Council's meeting agenda for adoption as an A-listed item (meaning for adoption without further discussion) on 8 February 1993.

8.3.2.5. Common Position

The common position was sent to the Parliament, who received it in March 1993 and presented their opinion, on the second reading in April, resulting again in an approval with amendments. The Commission's position on the Parliament's amendments on second reading was also published on the same date, as a partial agreement.

8.3.2.6. Re-examined Proposal

The Commission adopted a re-examined proposal and published this on the 1st of June with an explanatory memorandum stating that '*On the 21 April 1993 Parliament accepted the common position adopted by the Council on 8 February 1993 and proposed one amendment.*'[385, p.2] It also stated that '*This proposal takes into account the amendment proposed by Parliament which the Commission considers can be accepted in substance. The amendment will improve the definition of the scope of the directive.*'[385, p.2] The re-examined proposal was sent to the Council and to the Parliament, and was placed on the Council agenda for adoption without further discussion by on 14 June 1993. Figure

[i] whose rapporteur was José Valverde Lopez

[ii] The Opinion of ENVI and the report by ECON, Documents A3/1992/178; PE/153198/ECO/FIN, are not publicly available on the website.

8.6 summarises the procedure, which took just twenty-three months from when the proposal was first adopted by the Commission to its final publication in the OJ.

8.3.3. The Ordinary Legislative Procedure

The Ordinary Legislative Procedure, previously called 'co-decision', is the procedure through which most EU laws are now made. The ordinary legislative procedure is set out in the Treaty on the Functioning of the European Union (TFEU) in Article 294,[386] and it was this procedure that was applied to the MDR. It is a more complex procedure, with more steps and more options possible for each legislative step, so I will not describe it in detail, but it is summarised in Figure 8.6, sourced from the Guide to the Ordinary Legislative Procedure.[387, p.45]

It differs from the Cooperation Procedure in that the Council and the EP are co-legislators and there are two readings of the proposed legislation. The Commission also often holds a consultation phase before it submits a proposal, and a Conciliation Committee may be convened if agreement on a proposal cannot be reached. The procedure also allows for trilogues, which are meetings between small numbers of delegates from Parliament, the Council and the Commission (usually including the key people involved in drafting the legislative proposal or positions, and legal experts) to negotiate, report back to their respective delegations in the Conciliation Committee and facilitate reaching an agreement.

8.3.4. Enacting the MDR

The legislative history for the MDR is even more complex and drawn out than that of the MDD. It was initiated through a proposal from the Commission in September 2012. Opinions were sought from the ESC and the European Data Commissioner early in 2013, with the EP providing its opinion on first reading in October 2013, and again in April 2014. The Commission prepared its position on the EP's proposed amendments in July 2014, and thereafter there were multiple meetings between the preparatory bodies of the Council, with ten rounds of negotiation and two readings of the draft legislation before the MDR was finally enacted in May 2017.

The lead service drafting the legislation for the Commission in 2012, was the Directorate responsible for health, DG-SANTE, but by the time the MDR was enacted, this responsibility had been transferred to the Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs (DG-GROW), illustrating the tension between these two policy objectives within the Commission. The EP's lead committee was Committee on the Environment, Public Health and Food Safety (ENVI), whilst the

Section for the Single Market, Production and Consumption prepared the ESC opinion, and the Employment, Social Policy, Health and Consumer Affairs Council configuration (EPSCO) was responsible for negotiating the Council's position during the legislative procedure, illustrating the competing policy objectives, health and trade, amongst the different institutions.

8.3.5. Other legislative procedures

8.3.5.1. Special legislative procedure

The TFEU sets out a special legislative procedure, which may be used in specific cases, and it refers to legislative procedures where one institution acts (usually unanimously) after consulting the other. Mostly this procedure is followed by the Council after consulting the Parliament but may also occur the other way around. This procedure was not used for legislating medical devices so it will not be expanded upon further.

8.3.5.2. Non-legislative procedures

The Treaty of Lisbon introduced the concept of non-legislative acts, such as delegated or implementing acts, defining them as acts that do not follow either the ordinary or the special legislative procedure.[386, Article 290] Through these, the Commission has been given the power to amend or extend the legislative acts (e.g. directives[i]) that provide for this, as implementing or delegated acts, without requiring an Opinion of the EP or the Council, so long as it doesn't affect the 'essential requirements' set out in the original legislation.[386]

> *'1.A legislative act may delegate to the Commission the power to adopt non-legislative acts of general application to supplement or amend certain non-essential elements of the legislative act.*
>
> *The objectives, content, scope and duration of the delegation of the power shall be explicitly defined in the legislative acts. The essential elements of an area shall be reserved for the legislative act and accordingly shall not be the subject of a delegation of power. … The adjective 'delegated' shall be inserted in the title of delegated acts.'*[386, Article 290]

And …

> *'1.Member States shall adopt all measures of national law necessary to implement legally binding Union acts.*
>
> *2.Where uniform conditions for implementing legally binding Union acts are needed, those acts shall confer implementing powers on the Commission, or, in*

[i] This is only the case in those Directives where it specifies that the Commission has been given the authority to do this (i.e. it vests the power in the Commission to enact implementing or delegated acts, usually also specifying the scope of this power).

duly justified specific cases and in the cases provided for in Articles 24 and 26 of the Treaty on European Union, on the Council.

3.For the purposes of paragraph 2, the European Parliament and the Council, acting by means of regulations in accordance with the ordinary legislative procedure, shall lay down in advance the rules and general principles concerning mechanisms for control by Member States of the Commission's exercise of implementing powers.

4.The word 'implementing' shall be inserted in the title of implementing acts.' [386]

The Commission has used the power to introduce implementing acts on several occasions to supplement the medical device legal framework, for example for the designation and supervision of notified bodies, and establishing harmonised standards.[388–390]

8.4. Discussion

In summary, the MDD was enacted solely by the Council of the EEC in 1993, then a twelve-member community, using the cooperation procedure. The MDD was enacted at a time of when the EEC and its institutions were establishing and extending their power and authority. The primary rule-maker for the MDD was the European Commission. It proposed the text of the MDD, and although this was enacted by the Council, the Commission was the executive body responsible for its implementation at MS level. In contrast, the MDR was enacted by both the European Parliament and the Council of the EU in 2017, a twenty-eight-member community, using the ordinary legislative procedure, under which the EP and the Council are co-legislators.

At the time of the development of the MDD, the main regulatory focus of the Treaties was the creation of a free market for goods within the MS common market. This primary objective of increasing ease of trade for businesses and the flow of goods was reflected in the fact that the development of the MDD fell under the remit of the DG of industry. In fact, the lead working group involved in developing the MDD for each of the four regulatory institutions was the one representing industry. Health committees were consulted as 'associated services', however, they had little involvement (or effect) in the development process.

The revision of the MDDs followed public loss of confidence in the regulatory process to ensure the safety of medical devices being marketed in the EU. This is reflected in the fact that the Commission Directorate given responsibility for drafting the MDR proposal was DG-SANTE. However, over time, this safety focus lessened, whilst industry lobbied against a major redesign to the legal framework.[41,391,392] The regulatory process stalled,

and the responsibility for drafting the legal text shifted back to the Directorate responsible for industry (the Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, DG-GROW). However, in contrast to the MDD, the lead committee for the EP and the Council were those representing health concerns rather than trade, but it was still the industry section that took the lead in drafting ESC's opinion. Demonstrating that patient safety was a significant concern, but clearly not the only one, driving the revision of the legal framework.

Neither was enacted in a vacuum. International forces have also played a significant role as evidenced by the fact that the WTO requires its members to notify one another of any 'technical legislation' it plans to introduce that might affect trade or that doesn't adhere to international standards.[393, p.114] Furthermore, the EEC Commission, as a founding member, was involved in establishing the nascent GHTF at the time that the MDD was being proposed and enacted. This may explain the similarity between the GHTF Model Regulatory Framework and the regulatory approach taken in the MDD. However, it is less clear who influenced who. What is clear is that there have been multiple points of influence, much of it influenced by industry.

Furthermore, the dizzying array of institutions involved in the enactment of EU legislation, the variety of legislative procedures, and their complexity, makes it difficult for interested individuals to understand the legislative process, and therefore makes it difficult for them to exert any influence on it. In fact, to do so, they need to have the time, and other resources necessary to acquire this knowledge, which effectively precludes individuals or small interest groups from the policy-making process, supporting Stigler's assertion that '*the political system does not offer good incentives like those in private markets to the acquisition of knowledge*.'[145 p.11]

The MDD sets out a relatively complex set of rules regarding who implements and enforces the MDD, these will be the subject of the next two chapters.

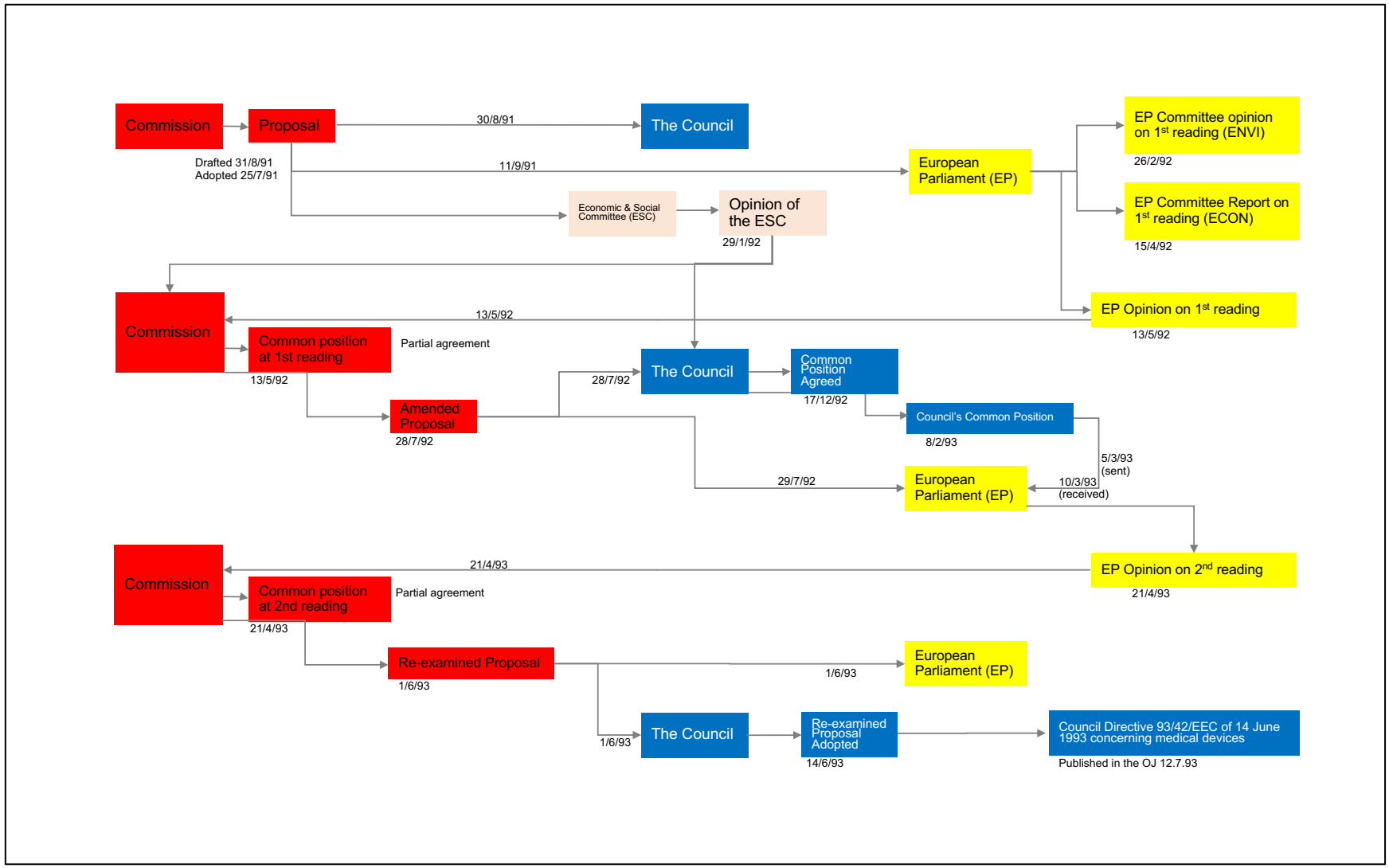

Figure 8.6. Legislative procedure enacting the MDD

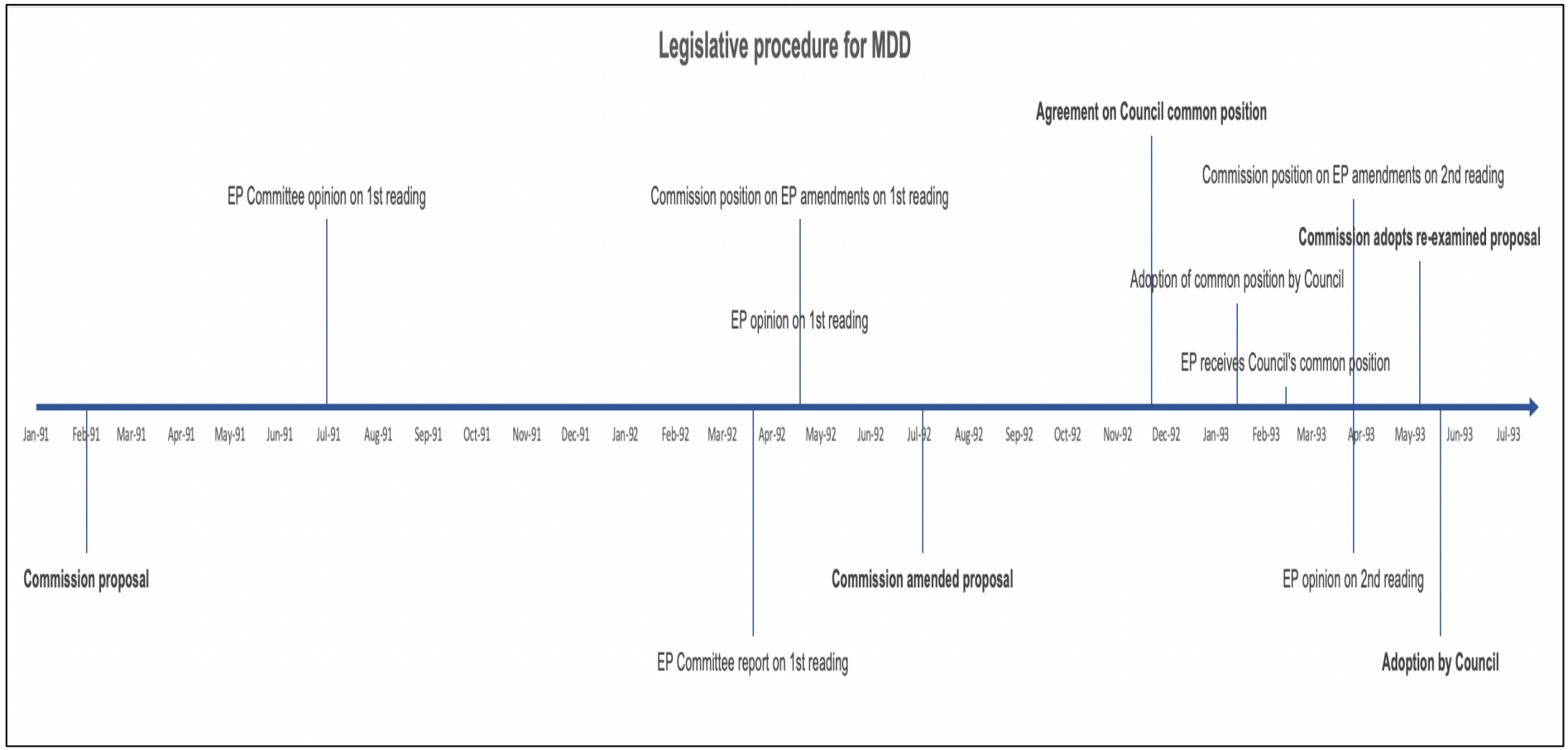

Figure 8.7. Enacting the MDD – Legislative Timeline

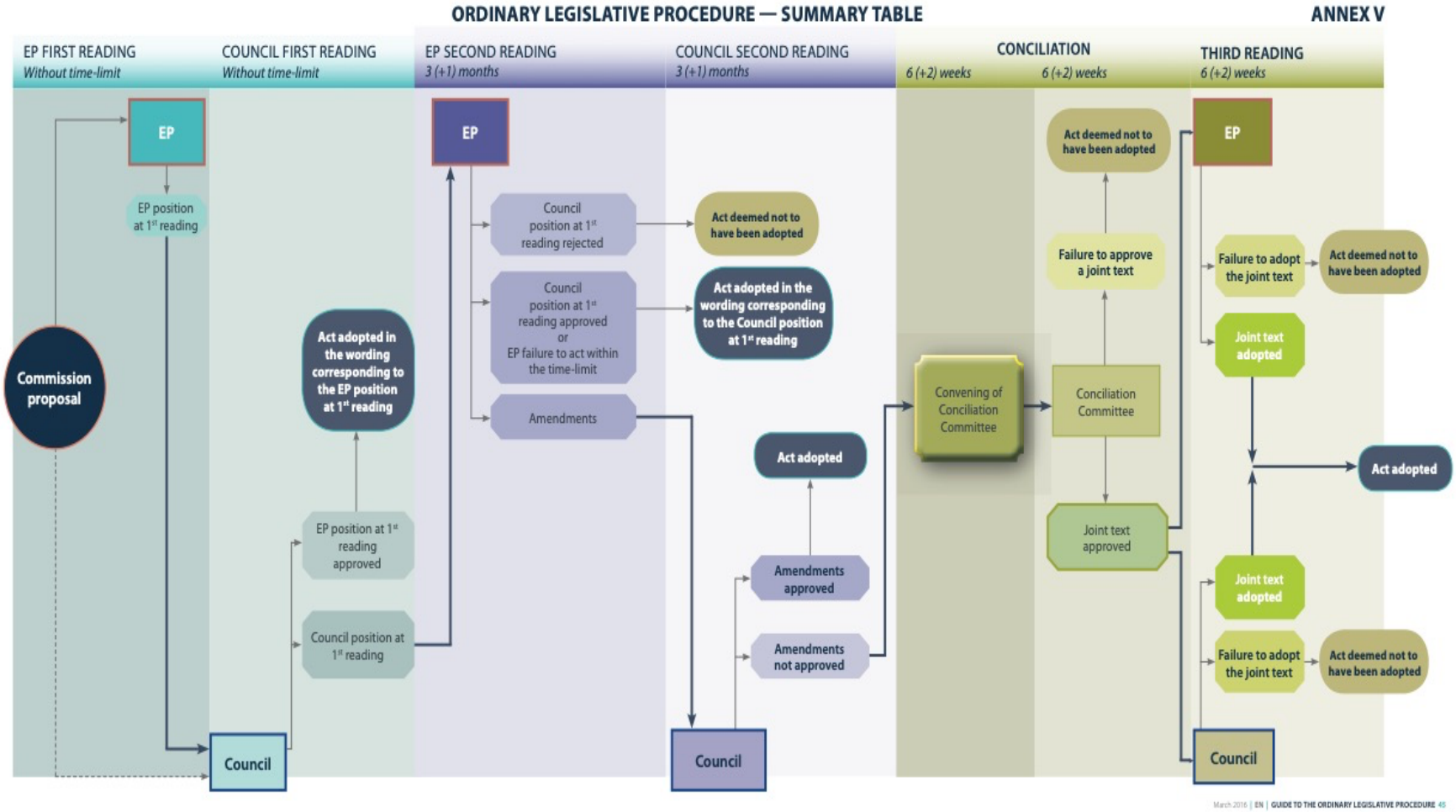

Figure 8.8. The Ordinary Legislative Procedure. Source: The Guide to the Ordinary Legislative Procedure, p.45

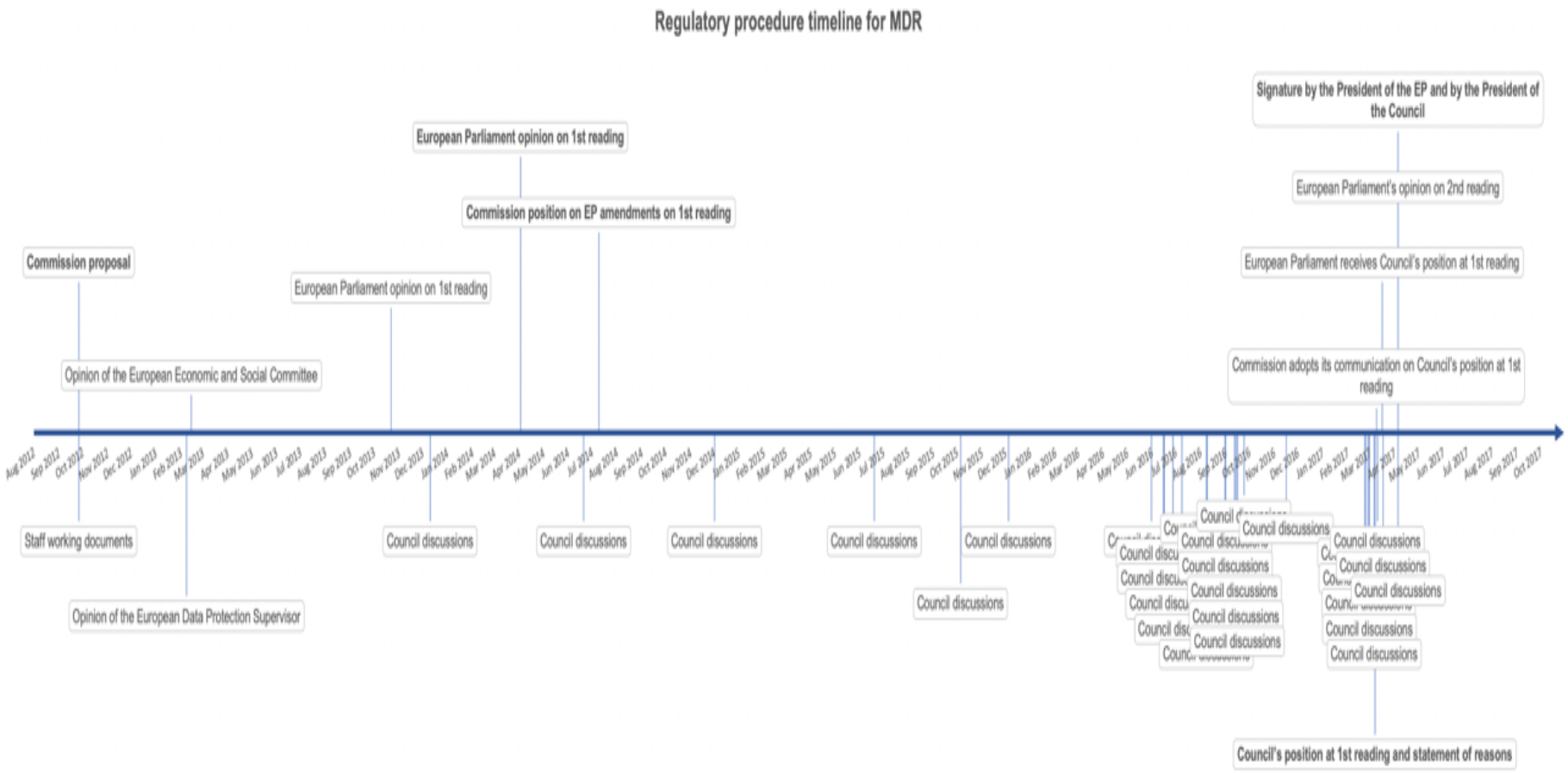

Figure 8.9. Enacting the MDR – Legislative Timeline

9. EU legal framework for medical devices

How are medical devices regulated? And how does this affect patient safety?

The objective of this chapter is to describe the legislation governing medical devices in the EU and explain how it came to be structured in this way, thereby explaining why it is the way it is and why it is not focussed primarily on ensuring the safety (including efficacy) of medical devices being placed on the EU market.

9.1. Legislative history influencing the MDDs

Having described how the MDD was enacted by the regulatory institutions, it is important to situate its enactment within the policy context of the period. This chapter describes the preceding legislative history that led to the development of the EU legal framework for medical devices and how it subsequently evolved, as this had a significant bearing on its goals, structure, and the contents of the legislation. Section 9.2 provides a brief account of the subsequent policy changes and legislation preceding the revision of the medical device legislation. This is followed by a description, in Section 9.3, of the original legal framework, providing details on the contents of the MDD. Section 9.4. describes the MDR, some of its key elements, and details some of the changes it introduces for patient safety. Section 9.5 concludes the chapter with a discussion on the goals of the legislation and the themes observed, and their effects on MD-PS.

9.1.1. The New Approach

The Treaty of Rome, enacted in 1957, envisaged a common market with free movement of goods, however, progress in achieving this was slow. Therefore, in 1969, the Council issued a resolution that it would act to remove barriers to trade that existed as a result of these differences in MS laws[i].[394] However, it wasn't until January 1985 that the Commission communicated its intention to harmonise the legal requirements for several broad categories of product across the MS.[395] Later that year, the Council issued Council Resolution of 7 May 1985 to take a '*new approach to technical harmonization and standards*' due to '*the urgent need to resolve the present situation as regards technical barriers to trade and dispel the consequent uncertainty for economic operators*',[383, preamble para 2] emphasizing the driving goal and underlying objective of these directives.

The Council Resolution stated that the 'new approach' would use European standards '*for the purposes of defining the technical characteristics of products*' and '*entrusting the task of defining the technical characteristics of products to standards … particularly as*

[i] Also published in the same issue of the OJ was the list of goods to be targeted for these new EEC laws, whose aim was to supersede MS product rules.[394]

regards health protection and safety'.[383, Annex I para 3, 4th indent] Rather than allowing MSs to individually govern these product categories, the Council resolved to introduce EEC legislation requiring MS to accept the marketing of these products if they met the '*essential safety requirements*' as embodied in harmonised standards. It was argued that by using agreed standards then the applicable standards would be the same in every country, thereby removing barriers to trade caused by differing laws and technical standards. The New Approach Directives were to specify the essential requirements[i] for a product type, which are the minimum requirements necessary for a product to be allowed on the market, but they are also the maximum necessary requirements, since MS were to be prohibited from demanding any further requirements beyond the 'essential requirements'.[395 p 11, 2nd point]

The Council Resolution of 7 May 1985 set out the principles guiding the 'new approach' and provided a standardised structure (see Box 9.1) for directives enacted under the new approach.[383] Directives were to be legally justified on the basis that, whilst MS are responsible for ensuring product safety, nevertheless, national safety requirements need to be harmonised to ensure free movement of goods. European Standardisation Organisations (ESOs) were the competent authorities for developing the harmonised standards to meet the essential safety requirements for products covered by the particular directive.[383, Annex II, Section 2]

Main elements (ε) to be included in the New Approach Directives

I. Scope
II. General clause for placing on the market
III. Essential safety requirements
IV. Free movement clause
V. Means of proof of conformity and effects
VI. Management of the list of standards
VII. Safeguard clause
VIII. Means of attestation of conformity
IX. Standing committee
X. Tasks and operation of the committee

Box 9.1: Main elements to be included in the 'New Approach' directives

The resolution also provided a list of criteria to guide which areas could be given initial priority for developing this new approach. Consequently, the New Approach Directives

[i] Most of which relate to the design and manufacture of a product, and the risks to be avoided or minimised.

were targeted at products where there was '*a lack of community activity at that time*'[i],[383 p.9, (c)2nd para]; prioritising areas covering a wide range of products that were considered to be sufficiently homogenous to enable definition of common essential requirements, distinguishable from manufacturing specifications, and where standards could be applied to the group of products[ii].[383]

Directives subsequently issued under this 'New approach' for specific product groups were given an EC or CE mark to indicate conformity with the relevant Directive.[396] The EC mark was replaced with CE Marking in 1993, to standardise the symbol indicating that a good or service met certain quality standards and essential legal requirements for goods and services being sold on the European market[iii].[397] It must be pointed out that it is generally assumed that CE marked devices are effective, but no mention is made regarding any requirements for effectiveness beyond the fact that a product must perform as intended by the manufacturer.

For medical devices this resulted in the development of the three Medical Device Directives (MDDs),[1,4,5] which, in line with the other harmonisation regulations, were originally conceived of as a means to ensure free movement of goods and fair competition, whilst '*maintaining or improving the level of protection achieved in Member States'*.[1, 5th recital]

9.1.1.1. Global approach

To further support the New Approach, Council issued a resolution in 1989 on 'a global approach to conformity assessment' that included a commitment to promote international trade,[398] followed in 1990 with Council Decision 90/683/EEC regarding the conformity assessment procedures to be followed,[399] which was updated and replaced in 1993 with Council Decision 93/465/EEC[400]. Together these pieces of legislation introduced a system of conformity assessment that relied on mutual recognition by relevant authorised bodies of technical standards, assessment procedures, and the use of a specific marking to indicate compliance with the requirements.

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[i] This may explain why medicines escaped the 'new approach', because EEC legislation already existed for medicines (i.e. Council Directive 65/65/EEC).

[ii] In fact, the three priority areas were products from mechanical engineering, building construction, and electrical appliances. This last one included electromedical equipment, which may be why active implantable medical devices were targeted, resulting in the Active Implantable Medical Devices Directive (AIMDD). It is possible that this inadvertently led to the inclusion of medical devices amongst the products being subjected to the new approach directives, because the Commission had previously stated that this approach was less appropriate for legislation protecting health as opposed to safety.[395, p.19]

[iii] It also served to indicate to MS that they could not prohibit or restrict the marketing of these products within their jurisdictions.

Table 9.1. Some key acts of the institutions enabling the 'New Approach'

Legislation	Known as or Document reference	Comment
Council Directive of 28 March 1983 laying down a procedure for the provision of information in the field of technical standards and regulations	Council Directive 83/189/EEC	Requires MS to inform the Commission and the ESOs of its standards programme (updated quarterly), including any draft national standards, explaining its reasons if the draft is new, an amendment, or incorporates '*certain national divergences*' into an international/European standard. These are to be discussed by the ESOs regarding whether it needs to incorporate any national drafts into its own work plan; and prohibiting MS standards bodies from further developing standards or technical requirements in that field until the ESOs have drawn up the European standard.
Communication from the Commission to the Council and to the European Parliament on 31 January 1985	COM(85)19 final	This proposes a new approach to technical harmonisation to eliminate trade barriers that uses a '"general reference to standards approach"', and sets out an outline for directives to be enacted under this new approach. Its approach is based on the 1973 'Low Voltage Directive'.
Commission Proposal for a Council Decision concerning the modules for the various phases of the conformity assessment procedures which are intended to be used in the technical harmonization directives	89/C 231/03	This sets out the proposed means of assessing products for their compliance with the essential safety requirements in the new approach directives.
Council Resolution of 7 May 1985 on a new approach to technical harmonization and standards	Council Resolution 85/C 136/01	This calls on the Commission to draft a proposal for the 'new approach' that it had suggested in its communication. It represents the proposed new approach for achieving the internal market through technical harmonisation and provides guidelines, principles, and the key elements to include in the new approach directives (it essentially adopted the Commission's Communication, COM(85)19 final).
Council Decision of 13 July 1987 laying down the procedures for the exercise of implementing powers conferred on the Commission	Council Decision 87/373/EEC	This establishes committees to assist the Commission, describing 3 legal procedures, which it must apply for enacting implementing legislation (which of the 3 is specified in the relevant Council legislation that the Commission is acting to implement). These procedures impose varying degrees of oversight and supervision of the legislation that the Commission is empowered to enact for implementing Council legislation. It also provides a 'safeguard procedure', which it must apply whenever it has to decide on safeguard measures to take.
Council Resolution of 21 December 1989 on a global approach to conformity assessment	Council Resolution 89/C 10/01	Council calls on the Commission to draft a proposal for a common approach for assessing the compliance of products with the essential requirements set out in the new approach directives to enable the mutual recognition of proofs of conformity by various MS and third countries.
Council Decision of 13 December 1990 concerning the modules for the various phases of the conformity assessment procedures which are intended to be used in the technical harmonization directives	Council Decision 90/683/EEC	This sets out the different procedures for assessing the compliance of products with the relevant 'new approach directive'. Manufacturers are given a choice, with varying degrees of scrutiny by external conformity assessment bodies.

The approach to assessing compliance – conformity assessment

A system of conformity assessment was established to provide a means of assessing the compliance of products with the specified essential requirements, and manufacturers were given a number of conformity assessment procedures (CAPs) to choose from to demonstrate conformity. The CAP is divided into two phases for assessment – design and production. A CAP must cover both phases, which may be conducted separately or within a single CAP.

Council Decision 90/683/EEC explains why the conformity assessment of medical devices as described in the MDDs are the way they are. It describes seven conformity assessment procedures, referring to them as Modules A, B, C, D, E, F, and G, subdividing the design and production phases into separate processes for assessment, so that the procedures (i.e. modules) may address either the design or the production phase, or both, and summarising them as shown in Figure 9.1.[399] Some modules involve external conformity assessment bodies (CABs) or notified bodies (NBs) to be involved in this process, in which case they also issue certificates attesting conformity to the aspects examined by them. According to NBOG guidance for NBs, Modules C and G are not used in the MDDs, so these will not be described here.[401]

Apart from **Module B**, each module describes the procedure that the manufacturer (or in some instances, their authorised representative) who meets the given requirements '*ensures and declares*' that the product conforms with the requirements of the directive.[399]

Module B is intended solely for assessing the design phase. Four modules (**C, D, E, and F**) are available for assessing solely the production phase. It is intended that whichever production phase module is used, it must be used in combination with Module B, assessing the design phase, to complete the conformity assessment procedure[i]. In addition, there are two modules available for assessing the entire design and production of a product, one that is solely the responsibility of the manufacturer (**Module A**), while the second, **Module H**, requires the involvement of a notified body in the conformity assessment procedure. These are illustrated in Figure 9.2.[402 p. 55]

[i] Except in cases where the design and production are very simple, then they may be used with using Module B.

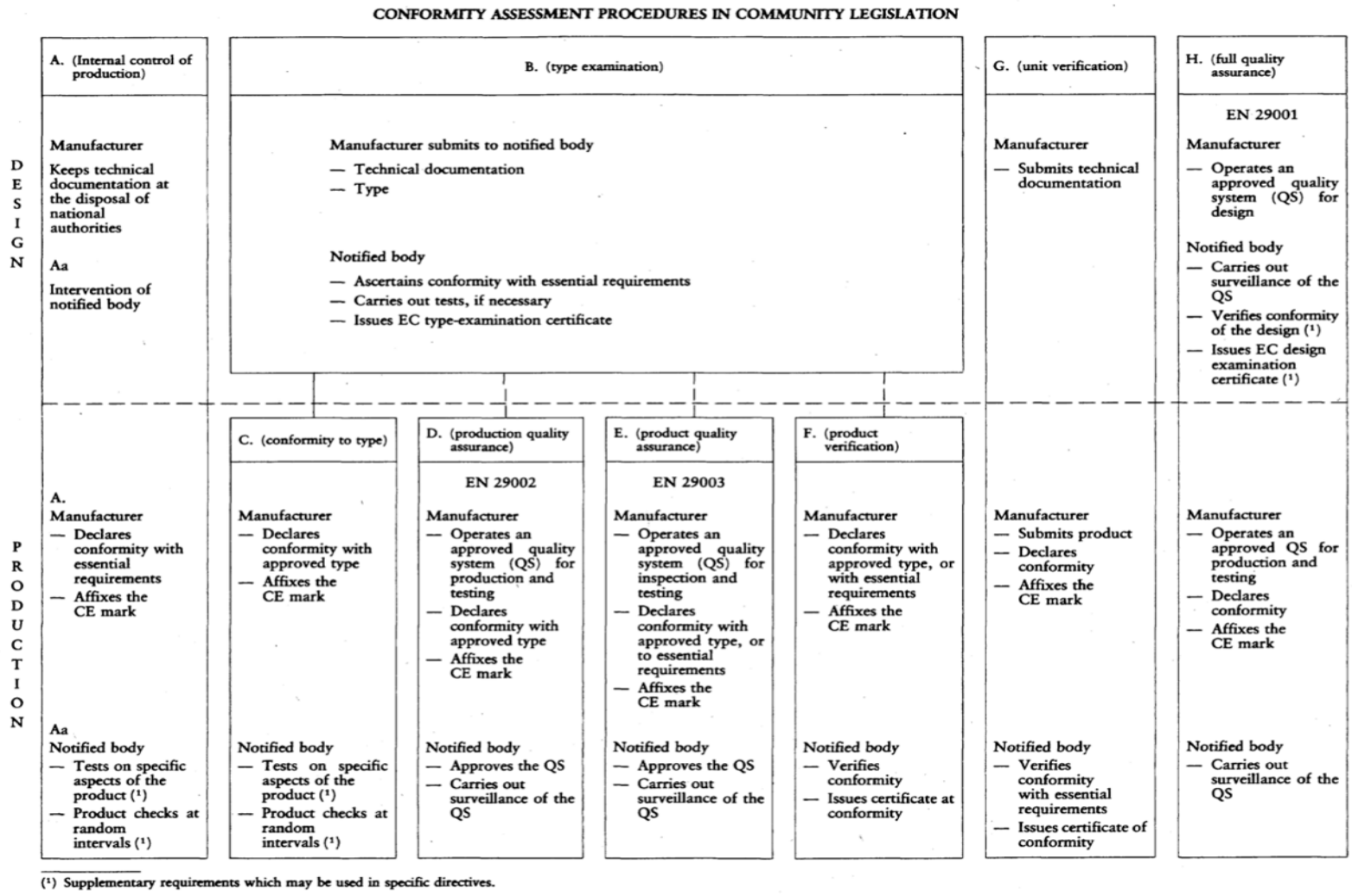

Figure 9.1. Conformity assessment modules introduced by Decision 90/683/EEC

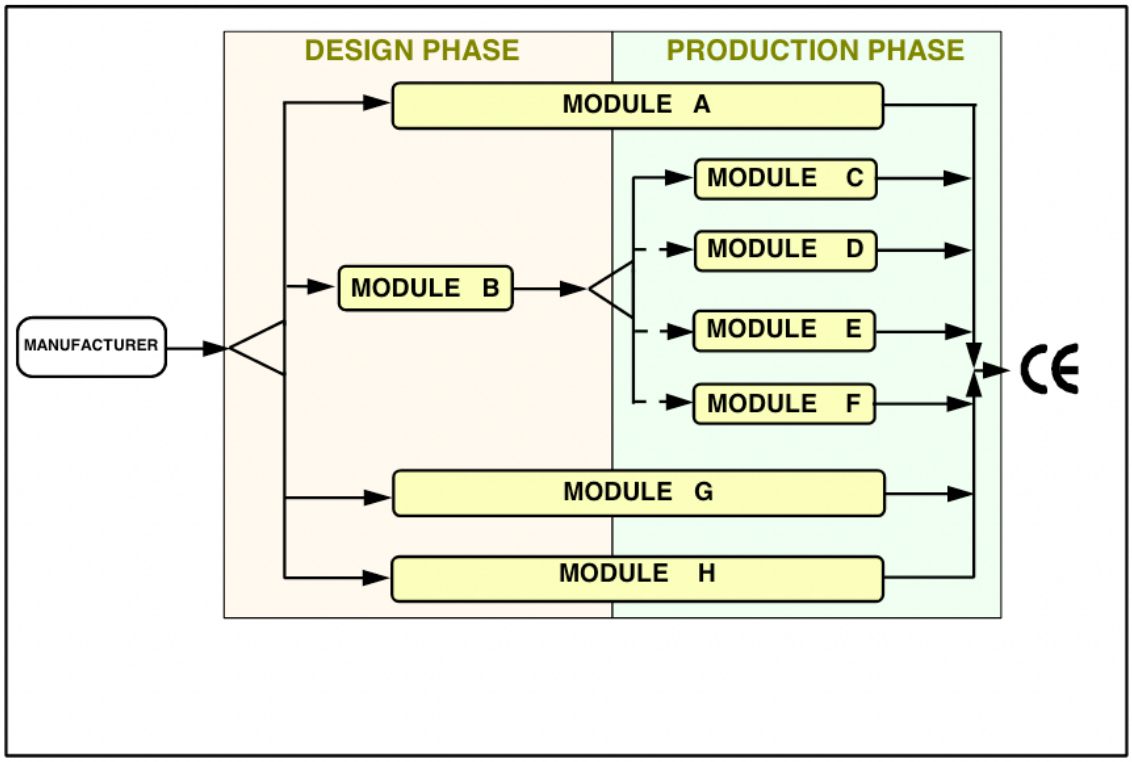

Figure 9.2. Conformity assessment modules (extract from the Guide to the Implementation of Directives based on the New Approach and Global Approach. [402 p. 55]

Module B describes the part of the conformity assessment procedure where a notified body (NB) checks and tests (or approves the manufacturer to test) that a representative *'specimen'* of the intended production process complies with the applicable requirements of the relevant product directive.[399, Module B (EC type-examination) (1)] On completion of this module the NB issues an EC type-examination certificate to the manufacturer.[i]

Each module requires the compilation of the product's technical documentation (listed in Table 10.3) needed to assess whether the product meets the requirements of the directive. **Modules D, E, and H** also require that a quality system (QS) be set up to control the final inspection and testing process (D, E, and H), the production process (E and H), and the design process (H). Each of these modules also requires the involvement of an NB to assess the QS for its adequacy in fulfilling the requirements of the directive regarding the applicable process(es) (design, production, and/or product inspection/testing). The QS or quality management system (QMS) is a documented control process.

For **Module E** this means that every product is examined and tested to ensure its conformity, whilst for **Modules D and H**, the QS is the *system* that the manufacturer uses

[i] The guide provided by the GHTF, 'Principles of Conformity Assessment for Medical Devices', explains that a 'type examination' means that one or more representative units of the device type chosen by the manufacturer, such as a prototype representative of the final production set up, together with its technical documentation is examined by the NB to confirm that it is compliant.

to ensure that products comply with the specified essential requirements (and, for **Module D**, to ensure that it also conforms to the type described in the EC type-examination certificate). All aspects of the QS must be systematically documented, using policies, procedures and instructions written in such a way as to ensure that everyone understands them in the same way. The QS must contain an adequate description of the elements listed in Table 9.2.

Modules A, B, and F do not require a QS, instead they require that the manufacturer keeps the technical documentation considered necessary to assess the conformity of the product with the directive. Box 9.2 lists examples of the types of technical documentation that are required.

Notified bodies are not generally involved in the conformity assessment procedure when Module A is applicable, but for all the other modules the manufacturer must apply to a notified body of his choice to either have the QS (**Modules D, E, and H**) or the product assessed in **Module F, or B if the type is a production type** (and for the sterilisation and/or measuring function if using Module A) assessed. Assessment of the manufacturer's QS is to determine if it meets the QS requirements relevant to the module (as listed in Table 9.2), and requires the assessment of the QS documentation (as listed in point 4 in Table 9.2) and the technical file, and an inspection of the manufacturer's premises. In addition, the NB must perform surveillance of the QS to ensure that manufacturers meet the obligations imposed on them by the QS.[399](**Modules D, E, H**: 4.1) The manufacturer must undertake to maintain the QS, meet the requirements it imposes, inform NBs of any changes in the QS[i], and allow NBs access to its premises (design, manufacture, inspection and testing, and storage sites, as relevant to the specific module) for inspection and audit, including access to the relevant documentation.

For **Module B**, the NB assesses whether the specimen has been manufactured in accordance with the specifications set out in the technical documentation. They also check whether the manufacturer has applied the standards described in the technical documentation, and where applicable standards have not been applied the NB assesses the alternative approach(es) used by the manufacturer to determine whether they meet the essential requirements using the appropriate examinations and tests.

Table 9.2. Quality system requirements for conformity assessment modules D, E, and H

QS requirements must include a description of:	Module E	Module D	Module H
1.The quality objectives	√	√	√

[i] NBs then assess if the change(s) still meet the requirements or if the amended QS needs a re-assessment.

2. The organizational structure, responsibilities and powers of the management regarding -	Product quality	Product quality	Product quality & Design
3. The examinations and tests that will be carried out -	After manufacture	Before, during, and after manufacture, and their frequency	Before, during, and after manufacture, and their frequency
4. the quality records, such as inspection reports, test data, calibration data, qualification reports of the personnel concerned, and other information as relevant	√	√	√
5. the methods for monitoring that -	the quality system is operating effectively	the quality system is operating effectively & the required product quality is achieved	the quality system is operating effectively, the required product quality is achieved, & the required design is achieved
6. Other controls or quality assurance methods	X	the manufacturing, quality control and quality assurance methods, and systematic actions that will be used,	the manufacturing, quality control and quality assurance methods, and systematic actions that will be used,
	X	X	the design control and design verification methods, and systematic actions that will be used for products in the product category covered,
	X	X	the technical design specifications, including standards being applied, and, if not being fully applied, the methods that will be used to ensure that the essential requirements will be met,

For **Module F**, the NB carries out tests to verify that products are compliant with the type they are derived from[i] and that they meet the essential requirements of the given directive. This may involve testing every product or a statistical sample of them.

In all of these modules, where harmonised standards have been used to meet an essential requirement or a specific part of a requirement the CAB or NB must presume that the product is in conformity with that. If other 'solutions' have been used to meet an

[i] That is that the prototype or sample specimen matches the design specifications detailed in the Type examination certificate.

essential requirement these must be assessed as to whether they are adequate for meeting the essential requirement.

On completion of the conformity assessment module (apart from Module B), manufacturers are required to affix a CE marking[i] to their product and draw up a declaration of conformity[ii] (DoC). The DoC states that the manufacturer assumes responsibility for compliance and that the device meets the requirements.

The content of the technical documentation shall be laid down directive by directive in accordance with the products concerned. As an example, the documentation shall contain so far as relevant for assessment: - a general description of the product, - conceptual design and manufacturing drawings and schemes of components, sub-assemblies, circuits, etc., - descriptions and explanations necessary for the understanding of said drawings and schemes and the operation of the product, - a list of the standards referred to in Article 5, applied in full or in part, and descriptions of the solutions adopted to meet the essential requirements of the directive where the standards referred to in Article 5 have not been applied, - results of design calculations made, examinations carried out, etc., - test reports.

Box 9.2. Required technical documentation

In summary, Modules D, E, and H utilise a QS, which must be approved by an NB to meet the essential requirements. Whilst Modules A, B, and F don't require the use of a QS. Instead they rely solely on technical documentation (which includes test results), requiring an NB to verify conformity with the essential requirements for Modules B and F (and sometimes specific aspects of A). Module B is conducted by the NBs to assess whether a representative specimen is in conformity with the design specified in the technical documentation. Module F involves verification of every product or product batch, or a sample of these, to confirm it meets the requirements. NBs conduct surveillance of the QS to ensure that the manufacturer is complying with the requirements imposed on them by the QS.

Thus, conformity assessment relies on assessing the technical documentation and an examination of a specimen representative of the production process or verification of the quality of each product or batch of products. This may also involve the assessment of the quality system used by the manufacturer for some or all of the design, manufacture,

[i] In the cases of modules D, E, and H, this must include the identification of the notified body who conducted the assessment of the QS.

[ii] The contents of this must include the list of contents shown in Box 9.2.

and end-product testing phases by a CAB/NB, who also inspects the manufacturing premises, audits their QS, and performs regular surveillance on it.

9.1.2. The not so 'new' approach

This 'new approach' was hardly 'new' as it drew on the approach the EEC had taken previously in other areas of trade where there were health or safety concerns. For example, Council Directive 64/432/EEC on animal health and Council Directive 64/433/EEC on fresh meat, both of which could pose health risks to humans, introduced measures to '*approximate'* MS laws, based on Article 100, primarily with the aim of removing barriers to trade.(2)(3) The recital to Directive 64/432/EEC stated that:

> '*Whereas Regulation No 20 substitutes for the numerous traditional means of protection at the frontier a single system designed in particular to facilitate intra-Community trade; whereas the regulation to be adopted for beef and veal is also designed to eliminate obstacles to such trade;*
>
> *Whereas, so long as intra-Community trade in bovine animals and swine is hindered by differences between the health requirements of Member States, the implementation of the above-mentioned regulations will not have the desired effect;*
>
> *Whereas, to eliminate those differences, measures must be taken … on the progressive establishment of a common organisation of markets ; whereas the animal health provisions of Member States must therefore be approximated;'*[403, Recitals 2-4]

Under this Directive, differences in health requirements were perceived as a barrier to trade and therefore the laws had to be 'approximated' (i.e. harmonised) to remove this barrier to trade between MS. This provides another example, from 1964, of the EEC's regulatory focus on increasing trade and the removal of any 'barriers to trade' caused by health/safety requirements. Furthermore, the Directive goes on to add that:

> '*Whereas the right of Member States under Article 36 of the Treaty to continue to apply prohibitions or restrictions on imports, exports or goods in transit justified on grounds of the protection of health and life of humans and animals nevertheless does not exempt them from the obligation to approximate the provisions on which those prohibitions and restrictions are based, in so far as the differences between those provisions hinder the implementation and functioning of the common agricultural policy;'*[403, Recital 5]

Thus health concerns were not allowed to interfere with this trade objective. This suggests that the primary goal was to remove barriers to trade, whilst health was of

secondary importance. This was also true in healthcare, as demonstrated in 1965 by the recitals in Council Directive 65/65/EEC on medicines :

> '*Whereas the primary purpose of any rules concerning the production and distribution of proprietary medicinal products must be to safeguard public health; Whereas, however, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community;*'[404, Recitals 2-3]

Whilst it suggests that safeguarding public health is the primary purpose, this must be done in a way that does not interfere with the development of trade and industry.

The approach taken to addressing safety in these earlier directives is also illustrated in the 1973 'Low voltage directive', which involved certain key elements that would be echoed in future directives with a similar purpose.[405] It focussed on:

- establishing product rules regarding the safety goals to be attained,
- providing a procedure to assess compliance,
- providing a safeguard mechanism (to restrict goods that were found to be unsafe) that was open to challenge, and perhaps most notably,
- requiring that the freedom of movement of compliant goods would not be restricted by any MS.

The directive didn't specify particular technical requirements, instead it relied on the development of technical specifications by standardisation bodies. The key elements are further expanded on in in Box 9.3.

These key elements are very similar to the criteria that were set out in Council's resolution in 1985 for the 'New Approach' directives, and, consequently, in the MDD. This is not really surprising as it appears that the Commission used it as a template for designing the 'New Approach'[i].[383 p.5]

Thus, the 'New Approach' directives, were a second tranche of directives aimed at removing barriers to trade, introduced after the expansion of the EEC. The New Approach was further facilitated by the enactment of the Single European Act (SEA), which provided an expedited legislative procedure through the introduction of QMV, which meant that the Council could more readily pass legislation since it no longer required the lengthy negotiations necessary to obtain a unanimous vote, nor could it be

[i] '*the Commission envisaged a gradual move towards basing further legislative efforts on the formula of the Low Voltage directive, experience of which had proved favourable. Safety provisions would be established to which products would have to conform, while the task of defining technical characteristics of products would be left to European, and if necessary, national standards.*' [395, p.5]

blocked by the preferences of a single nation. The result was that by 2000 the New Approach had been applied to at least seventeen different product categories, including medical devices, for which three main directives were enacted – the Active Implantable Medical Device Directive (AIMDD), the Medical Device Directive (MDD), and the In-vitro Diagnostic Medical Device Directive (IVDMDD), and subsequent amending directives. In this way the internal market did in fact become a common market.

1. The directive's scope was defined.
2. MS were held responsible for ensuring that only safe goods entered their markets. MS were also held responsible for ensuring that freedom of movement of compliant goods was not restricted.
3. Product rules, including the essential safety requirements regarding their safe design and manufacture, with which electrical equipment must comply were set out (in Annex I).
4. Products meeting these requirements must be allowed to enter all MS markets, and no MS could restrict the free movement of compliant goods because of their national standards.
5. Goods were to be considered compliant with the essential requirements if they used:
    - Harmonized European standards
    - International rules established by the International Commission on the Rules for the Approval of Electrical Equipment or the International Electrotechnical Commission (if there was no harmonized standard)
    - Mutual recognition of the national laws of the manufacturer's member state (if there was no harmonized standard and if it '*ensures a safety level equivalent to that required in their own country*'[405, Article 7])
    - Other means to demonstrate compliance
6. The assessment of compliance must be conducted using a prescribed conformity assessment procedure, which entailed the manufacturer:
    - preparing the technical documentation related to the design and manufacturing process showing that the product meets the essential safety requirements
    - drawing up of a declaration that the product conforms to the essential requirements
    - applying a CE marking to indicate that the product has undergone and passed a conformity assessment procedure.
7. Establishing a safeguard mechanism to allow MS remove or restrict unsafe products, and a means for other MS to object to such restrictions.
8. The requirement that MS inform the Commission of the authorities designated to carry out the tasks required by this directive (i.e. standards bodies, certification bodies, and conformity assessment bodies).

Box 9.3: Key elements of Council Directive 73/23/EEC, the low voltage directive

9.2. Legislative history influencing the MDRs

9.2.1. New Legislative Framework

In 2008, the New Approach was revised and updated, becoming the 'New Legislative Framework' (NLF). It consisted of two new Regulations and a Decision, supplementing the New Approach and the Global approach legislation: Regulation (EC) 765/2008, Regulation (EC) 764/2008, and Decision 768/2008.[406–408]

9.2.1.1. Council Decision 768/2008

Council Decision 768/2008 provided a common framework for the marketing of products by setting out the obligations of the various economic operators[i] involved in marketing products (i.e. manufacturers, authorised representatives, importers and distributors), the steps required for CE marking (including a variety of conformity assessment procedures that may be used), and the obligations of the various authorities[ii] involved in regulating specific sectors or categories of product.[406]

The means of attestation of conformity remained the same as it was in the New Approach Directives – the manufacturer's Declaration of Conformity (DoC), which the manufacturer must draw up as part of or on completion of the conformity assessment procedure. The contents of the DoC were also standardised and set out in Decision 768/2008/EC (Box 9.4).

9.2.1.1. Regulation (EC) No 764/2008

Regulation (EC) No 764/2008 drew on the principle of mutual recognition[iii] to remind MSs that it is illegal to prohibit goods from being placed on their markets (having the effect of being quantitative restrictions), unless there are safety risks or other reasons as set out

[i] Chapter R1, Article 1 provided definitions for the various economic operators:
3. 'manufacturer' shall mean any natural or legal person who manufactures a product or has a product designed or manufactured, and markets that product under his name or trademark;
4. 'authorised representative' shall mean any natural or legal person established within the Community who has received a written mandate from a manufacturer to act on his behalf in relation to specified tasks;
5. 'importer' shall mean any natural or legal person established within the Community who places a product from a third country on the Community market;
6. 'distributor' shall mean any natural or legal person in the supply chain, other than the manufacturer or the importer, who makes a product available on the market;
7. 'economic operators' shall mean the manufacturer, the authorised representative, the importer and the distributor;

[ii] These included the competent authorities (CAs), accreditation bodies (ABs), designating/notifying authorities, and notified bodies (NBs).

[iii] which means that if a good is legally marketed in one MS then it may lawfully be placed on the market in another MS

in Article 30[i] of the Treaty establishing the European Community.[409] In such circumstances, the competent authorities may still cause barriers to trade by imposing requirements on goods that have safety risks.[ii] It sets out the applicable procedure for competent authorities to prohibit market entry, withdraw a product, or place additional requirements on it prior to allowing it enter a nation's market solely for the purpose of safeguarding consumers, the environment, or another of the reasons listed in Article 30 of the Treaty.[408]

According to Decision 768/2008/EC the EC Declaration of Conformity should contain the following items :

1. the product number
2. the manufacturer's or his authorised representative's contact details
3. the statement:- "this declaration is issued under the sole responsibility of the manufacturer [or installer]:..."
4. product identifying features , which may include a photo, in order to aid traceability
5. the statement:- "the object of the declaration described above is in conformity with the relevant community harmonisation legislation: ……..... "
6. references to harmonised standards used or specifications ("in relation to which conformity is declared")
7. where applicable the notified body ... [name and number] performed... [description]... and issued the certificate...
8. additional information find for and on behalf of:...

(place and date of issue)(Name, function)

(signature):….

Box 9.4. List of required contents for the Declaration of Conformity

A national competent authority may also request information from the economic operator. If it intends to act to restrict, withdraw, or prohibit a product from the market, it must send a written notice to the economic operator of its intended action. It must justify its decision on the basis of a specific public health interest (i.e. the risk that the product poses to public health, morality or security, or the environment), with evidence for their concern and that the intended action is no more than is necessary to address the public interest of concern.

[i] '*Article 30: The provisions of Articles 28 and 29 shall not preclude prohibitions or restrictions on imports, exports or goods in transit justified on grounds of public morality, public policy or public security; the protection of health and life of humans, animals or plants; the protection of national treasures possessing artistic, historic or archaeological value; or the protection of industrial and commercial property. Such prohibitions or restrictions shall not, however, constitute a means of arbitrary discrimination or a disguised restriction on trade between Member States.*'(Article 30 of the Treaty of Rome, as amended – 'the Treaty')

[ii] Or other lawful reasons under Article 30 of the Treaty for restricting goods.

9.2.1.2. Regulation (EC) No 765/2008

Regulation (EC) No 765/2008 harmonises the requirements regarding accreditation, requiring MS to recognise the authority of accreditation bodies across the EU, which meant accepting the authority of accredited CABs.[407] It also set out the conditions and requirements to be placed on accreditation bodies and CABs, and on the surveillance of products placed on the market.

The EU claimed that the New Legislative Framework: improved market surveillance; set clear rules for the accreditation of CABs; improved the quality of the conformity assessment process, boosting confidence in it; enhanced credibility in the CE marking by clarifying its meaning; and provided a toolbox of definitions and procedures for future legislation to align with the new legislative framework.[410] The last point is probably the most crucial to note, as this was the reason for introducing the new legislative framework.[i]

9.2.2. Other influences on the Regulatory process

9.2.2.1. Lobbying

Ireland is one of only seven EU MS that have passed legislation on lobbying, the others being, France, Lithuania, Austria, Poland, Slovenia, and the UK.[411] Notably absent is Germany, which produces the largest share of the EUs medical device technology exports.[412] These seven countries and the Netherlands have lobbying registers whose completion is mandatory.[411] Germany, Italy, Croatia, and Romania also have lobbying registers but their use is voluntary. The EP is pushing for greater transparency.[411] Nevertheless, there remains a lack of transparency regarding corporate lobbying and its effects on legislation developments, though its effects may be felt.[41]

9.2.2.2. National influences

According to Altenstetter, the development of the medical device directives were influenced greatly by France, Germany and the United Kingdom (UK), each of which already had stronger regulatory requirements for medical devices than the other MS.[140, p.111] These nations were also significant producers of medical devices for the global

[i] The first recital for Decision 768/2008 states that '*On 7 May 2003 the Commission issued a Communication to the Council and the European Parliament entitled 'Enhancing the Implementation of the New Approach Directives'. In its Resolution of 10 November 2003 (3), the Council acknowledged the importance of the New Approach as an appropriate and efficient regulatory model allowing technological innovation and enhancing the competitiveness of European industry, and confirmed the necessity of extending the application of its principles to new areas, while recognising the need for a clearer framework for conformity assessment, accreditation and market surveillance*.' Thereby, clearly explaining the rationale for introducing the new legislative framework, which was to encourage innovation and competitiveness of European products.

market.[140, chapter 2] Their agendas were slightly different, but following the HIV-infected blood scandal and its political aftermath in France in the early 1990's, greater emphasis was placed on ensuring the safety of medical devices. This in turn influenced the development of the medical device directives as is seen in recital 18 of the original directive, which specifically mentions the risk of transmitting Acquired Immuno-Deficiency Syndrome (AIDS), the only clinical condition that is specifically mentioned in the MDD. [1, Article 18 413,414]

9.2.2.3. Saliency

Another influence at the time of the development of the medical device directives was the emergence of Bovine Spongiform Encephalitis (BSE) or 'mad cow disease' as it became known as. In the late 1980's, no known transmission to humans had occurred, nevertheless it was regarded by some as a public health threat and potentially the cause of a similar disease, variant Creutzfeld-Jacob Disease (vCJD) in humans.[415] Its influence is seen in Annex I of the MDD[i], where, originally it was stated that one of the risks to be avoided was infection with viruses, but this was later amended to include the risk of infection with 'transmissible agents'.[374, Article, Annex II, 1(f)]

Following the scandal of the Poly Implant Prothèse (PIP) breast implant, which highlighted the lack of regulatory control, renewed attention was paid to the medical device directives, resulting in the PIP Action Plan in 2012. This aimed to increase the scrutiny of notified bodies, introducing stricter rules for notified bodies, increased surveillance and product vigilance, and better communication and transparency.[416] The PIP scandal, resulted in calls for regulatory reform, and with the problems associated with metal-on-metal hip implants, pressure for reform increased.[15,18,18,417,391,418] This resulted in new medical device regulations being proposed and drafted by the Commission in 2012. The legislative procedure was long and drawn out[ii]. The new regulations were finally enacted in two parts and adopted in May 2017, coming into full force following a transition of five years for part one on medical devices (MDR), and in seven years for part two on *in-vitro* diagnostic devices (IVDR).[2,3] However, on 3 April 2020, with the MDR due to come into full effect on 26 May, the EU Commission proposed that the MDR be postponed for another year due to the SARS-CoV pandemic (Covid-19), so as not to risk a shortage of the medical equipment or devices needed to tackle Covid-19, and to avoid putting additional strain on health services.[419] The EU Parliament

[i] In point 8, para 3.

[ii] Potentially, partly due to the EP elections occurring in 2014, which resulted in changes in the party-political structure of the EP and its parliamentary committees involved in drafting positions.

adopted the proposal of the EU Commission, and Regulation (EU) 2020/561 amending Regulation (EU) 2017/745 was published in the OJ on the 24th of April 2020.[420] [421]

9.2.2.4. Interactions with other nations

Mutual recognition agreements (MRAs) are bilateral trade agreements that set out the conditions under which a non-EU country will the accept conformity assessments conducted in the EU as indicating compliance with their own regulatory requirements for a given product category, in this case medical devices, and vice versa. These conformity assessments require the designation of CABs by both parties to the agreement. In the EU the notified bodies are the designated CABs. The MRAs contain the list of agreed designated CABs, laboratories, and inspection bodies.

In addition to the MRAs, the Commission is represented at meetings of the IMDRF, and previously the GHTF, where they participate in developing harmonised regulatory guidance.

9.3. The original legal framework

The original (EEC) legal framework for medical devices consisted of the three medical device directives (AIMDD, MDD, and IVDMDD), subsequent amending legislation listed in Box 9.5, and implementing legislation.

As the applicable directive governing non-active implantable devices is the MDD, this section will provide a description of the rules contained in the MDD as it was originally enacted, comparing them with the key elements of the New Approach Directives, and exploring what they mean for medical devices, particularly regarding patient safety and the evidence available for evaluating device safety and efficacy.

- Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998[5]
- Directive 2000/70/ EC of the European Parliament and of the Council of 16 November 2000[371]
- Directive 2001/104/ EC of the European Parliament and of the Council text with EEA relevance of 7 December 2001[372]
- Regulation (EC) no 1882/2003 of the European Parliament and of the Council of 29 September 2003[373]
- Directive 2007/47/EC of the European Parliament and of the Council text with EEA relevance of 5 September 2007[374]

Box 9.5. List of legislation amending the MDD

9.3.1. Overview of the Medical Device Directive (MDD), 1993

The MDD contains twenty-two recitals, describing the rationale for the legislation, twenty-three Articles, specifying the rules, and twelve Annexes, which describe how the rules

should be applied. It also includes nine definitions in the original and fourteen in the amended versions. The contents of the MDD, described below, are listed in Table 9.3[i].

9.3.1.1. Recitals

In keeping with the reason for all the New Approach Directives, the main reason given for introducing the MDD is that it was needed to further the completion of the internal market to allow the free movement of goods, persons, services and capital. It also explains that differences between MSs market entry rules on a device's safety, health protection, and performance requirements create barriers to trade by limiting the free movement of these products within the common market:

> '*Whereas the content and scope of the laws, regulations and administrative provisions in force in the Member States with regard to the safety, health protection and performance characteristics of medical devices are different; whereas the certification and inspection procedures for such devices differ from one Member State to another; whereas such disparities constitute barriers to trade within the Community;*
>
> *Whereas the national provisions for the safety and health protection of patients, users and, where appropriate, other persons, with regard to the use of medical devices should be harmonized in order to guarantee the free movement of such devices within the internal market;*'[1, Recitals 1-3]

Thereafter, it distinguishes between what comes under the scope of the MDD and what doesn't, including how it relates to medicines, blood-derived products, human or animal tissue, and medical equipment, and specifically reassuring MS that healthcare funding decisions remain under their remit. Most of the remaining recitals explain the content of the MDD, rather than why it was enacted. These include justifying the use of essential requirements, which all devices must meet, and beyond which MS cannot demand more; the use of technical standards as a means of complying, and assessing compliance, with the essential requirements; the establishment of European Standardisation Bodies to develop and approve standards applicable to the New Approach Directives; and a system for assessing the design, manufacturing and packaging of medical devices.

Specifically justified is the need to classify devices according to their level of risk (rather than product category[ii]) to determine the applicable level of regulatory control and

[i] The symbol ε is used to indicate that it is a New Approach element, and which one is identified by the Roman numeral given to it in Box 9.1, whilst ∉ indicates that it is not an element of the New Approach directives.

[ii] From a legal perspective, there are just three 'categories' of medical device: *in-vitro* diagnostic devices; active implantable devices; and devices that are neither of these

scrutiny proportionate to the device's risks; and justifying the need to apply the most rigorous of the conformity assessment modules available under the New Approach Directives.[399]

9.3.1.2. Articles

The key elements of the New Approach Directives are listed in Box 9.1[i]. As can be seen from Table 9.3, it follows a similar pattern to the Low Voltage Directive and the structure planned for all New Approach Directives, containing the ten elements (ε) recommended by the Commission and included in the Council Resolution.[383]

The scope of the Directive is defined (Article 1) and responsibility is placed on MS to only allow devices that are safe and conform to the Directive onto the market (Article 2), whilst at the same time constraining them from prohibiting or restricting their marketing if they bear a CE marking (Article 4). MS are required to presume conformity for those essential requirements (or parts thereof) where harmonised standards have been applied, accepting them as proof of conformity (Article 5).

Manufacturers or their authorised representatives must ensure that '*devices must meet the essential requirements set out in Annex I which apply to them, taking account of the intended purpose of the devices concerned*.'[1, Article 3] Whilst the standards to assist with meeting the essential requirements are to be prepared by standards bodies (usually European Standards Organisations (ESOs) rather than national bodies to prevent barriers to trade), with lists of harmonised standards being published in the OJ (Article 6).

A safeguard clause is included that provides a means for MS to restrict unsafe devices being marketed in their territories whilst also preventing them from using this as a means of protecting domestically produced devices, by requiring that immediately inform the Commission, justify their actions, and explain whether the restrictions are needed due to: the essential requirements not being met; the incorrect application of harmonised standards; or inadequacy of the standards (Article 8).

The allowable CAPs, which are the means of proof of conformity, are provided in Article 11 and detailed in Annexes II-VII. They are modifications of the conformity assessment modules described in Decision 90/683/EEC,[399] with the modifications being justifies in the 14th recital, '*… justified by the nature of the verification required for medical*

[i] Main elements to be included in the New Approach Directives: I. Scope; II. General clause for placing on the market; III. Essential safety requirements; IV. Free movement clause; V. Means of proof of conformity and effects ; VI. Management of the list of standards; VII. Safeguard clause; VIII. Means of attestation of conformity; IX. Standing committee; X. Tasks and operation of the committee. These key elements are indicated in Table 10.4 by ε plus the element number in superscript.

devices;'[1, 14th recital] Article 11 limits the choice of conformity assessment modules made available to medical device manufacturers by the level of risk the device poses to patients or others. It thereby, requires a system for classifying devices according to their risk, and classification rules are provided in Annex IX.

The 'means of attestation of conformity' is provided for in Article 17 via the obligation to affix the CE marking on conforming device, supplemented by Article 18, which describes what MS must do in the case of the CE marking being wrongly affixed. As CE marking sometimes requires the intervention of '*National bodies authorised to issue marks or certificates of conformity*'[383, p.7], the notification procedures required for designating the notified bodies specifically for assessing medical devices are set out in Article 16, and in Annex XI.

The standing committee, and its applicable tasks and operations (i.e. rules of procedure), to assist the Commission in implementing this directive are set out in Article 7.

A mechanism for manufacturers to appeal decisions made by any MS to restrict their products, is also provided (supplementing provisions in Articles 2, 4, 8) that mandates MS to inform them (and explain their reasons) in advance of any actions the MS plans to take to restrict the free movement of their devices (Article 18).

As also envisaged within Decision 90/683/EEC,[399 the Annex, I(i)] a provision for maintaining the confidentiality[i] of the information obtained by notified bodies during the performance of their tasks is included in Article 20[ii].

The last three article, Articles 21-23, are administrative requirements, repealing and amending other legislation affected by the MDD, providing implementation timelines and transitional provisions, and concluding with, '*This Directive is addressed to the Member States*',[1, Article 23] which makes it very clear who the regulatory target is.

Four Articles and two Annexes were not directly envisaged within the scope of the New Approach Directives, but were justified in the recitals:[iii] Articles 10 (information on incidents); 12 (procedures for systems and procedure pack); 14 (registration of persons responsible for placing devices on the market); 15 (clinical investigations); Annex VIII (statement concerning devices for special purposes); and Annex X (clinical evaluation), each of which is described below.

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[i] Annex to 90/683/EEC '*(i) in order to protect the manufacturers, the technical documentation provided to notified bodies has to be limited to that which is required solely for the purpose of assessment of conformity. Legal protection of confidential information shall be required;*'[399 the Annex, I(i)]

[ii] In fact this goes even further in the MDD, which states that '*Member States shall ensure that <u>all the parties</u> involved in the application of this Directive are bound to observe confidentiality with regard to all information obtained in carrying out their tasks.*'[1, 14th recital] (emphasis added)

[iii] The fact that these are not key elements is indicated in Table 10.4 by (∉).

Table 9.3. List of Articles and Annexes of the MDD

Article	Heading
Article 1	Definition and scope[εI]
Article 2	Placing on the market putting into service[εII]
Article 3	Essential requirements[εIII]
Article 4	Free movement[εIV]
Article 5	Reference to standards[εV]
Article 6	Committee on Standards and Technical Regulations[εVI]
Article 7	Committee on Medical Devices[εIX]
Article 8	Safeguard clause[εVII]
Article 9	Classification[εIII]
Article 10	Information on incidents (∉)
Article 11	Conformity assessment procedures[εV]
Article 12	Procedures for systems and procedures packs[εIII]
Article 13	Decisions re classification and derogation clause[εIII]
Article 14	Registration of persons responsible for placing devices on the market (∉)
Article 15	Clinical investigation (∉)
Article 16	Notified bodies[εVIII]
Article 17	CE marking[εVIII]
Article 18	Wrongly affixed CE marking[εVIII]
Article 19	Decision in respect of refusal or restrictions[εIV]
Article 20	Confidentiality
Article 21	Repeal and amendment of directors
Article 22	Implementation, transitional provisions
Article 23	This Directive is addressed to the Member States
Annexes	**Title**
Annex I	Essential requirements[εIII]
Annex II	Declaration of conformity[εV] (full quality assessment system)
Annex III	EC type examination[εV]
Annex IV	EC verification[εV]
Annex V	EC declaration of conformity[εV] – production quality assessment
Annex VI	EC declaration of conformity[εV] – product quality assessment
Annex VII	EC declaration of conformity[εV]
Annex VIII	Statement concerning devices for special purposes (∉)
Annex IX	Classification criteria[εIII]
Annex X	Clinical evaluation (∉)
Annex XI	Criteria to be met for the designation of notified bodies[εVIII]
Annex XII	CE Marking of Conformity[εVIII]

Information on incidents (Article 10)

MS are required to record and evaluate any information on medical device-related incidents (that they become aware of) centrally if there is '*any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use…*' leading to (or might have led to) either the death, or a serious deterioration in health, of a patient or user or a systematic recall of a type of device. However, it does not require MS to actively and systematically collect such data, instead they must record and evaluate the information that they become aware of, mostly through mandatory reporting by manufacturers of serious incidents (or near misses that could have had serious results) that they become aware of and through voluntary reporting by healthcare providers. The recording and evaluation on non-serious AMDEs is not legally required, though this would be important information for doctors and patients (if it were made available).

Procedures for systems and procedure packs (Article 12)

This provides rules for determining who is legally responsible when systems[i] or procedure packs[ii] are put together and the rules that they must follow to place them on the market. Similar to manufacturers of other devices, the entity responsible for combining devices into a system or procedure pack must draw up a declaration, but in this case they are declaring that they have combined CE marked devices together as intended by the original manufacturers and followed their instructions in the process, supplying the relevant instructions for each part, and applying the appropriate internal control and inspection processes. When this involves a sterilisation process, then the system or procedure pack producer must apply to a notified body for assessment of their compliance (according to Annex IV, V or VI) with the essential requirements related to sterilisation. In cases where, for some reason, they have not followed the manufacturers' instructions or if the combination of devices includes a non-CE marked device, then this

[i] These include devices used in combination, which usually depend on being combined in order to function. For example, the stacks used in theatre that provide light and video the interior of the body; endoscopy systems that include the tubing, endoscopic lighting, camera, gas tubing, and the monitor; imaging systems connecting x-ray emitters to receivers, transmitting these to monitors; angiography and angioplasty systems that connect the equipment for visualising heart vessels to the monitors, and includes tubing for introducing dye, or equipment for measuring the intraarterial flow rate, and/or the introducer for implanting stents. The successful operation of these systems relies on all the parts being compatible and functioning together as they should.

[ii] These are sterilised packs of instruments and other requirements, such as swabs, sterile gowns, gloves, etc, which are used during surgical procedures. Therefore, one of the main risks associated with these is the risk of contamination leading to infection.

must be considered as a device in its own right, which requires full application of the MDD to the pack or system, including conformity assessment and CE marking.

Registration of persons responsible for placing devices on the market (Article 14)

Manufacturers (or their authorised representative (AR)) of Class I devices, custom-made devices, or those who put devices together into systems/procedure packs must register their place of business with the national competent authority (NCA) in those MS where they are placing their devices on the market. They must also supply a description of the devices that they are placing on the market. This registration requirement is not placed on manufacturers, or their ARs, of higher risk devices[i], which means that the NCAs do not have a list of manufacturers/ARs or descriptions of the higher risk devices available on their market.

Clinical investigations (Article 15)

As it is illegal to put non-compliant devices on the market or to make them available for use, this Article provides a mechanism for using non-CE marked devices in a clinical investigation by notifying the NCA of the MS where the investigation is to be conducted, following the procedure set out in Annex VIII. Clinical investigations must be conducted in compliance with Annex X.

9.3.1.3. Annexes

This section describes the Annexes[ii], concentrating on Annexes I, VIII, IX, and X. Annexes II-VII contain the various modules made available for conducting conformity assessment. These will be further explored in the section on implementation. Annex XI describes the tasks and requirements placed on notified bodies, whilst Annex XII describes the affixing of the CE marking and its dimensions.

The Essential Requirements (Annex I)

Annex I sets out thirteen essential requirements (ERs), as illustrated in Table 9.4.[iii] ERs 1-6 are general requirements, which, together with and ER13 are applicable to all devices. The others (or parts of them) apply only to certain devices. For example, ER10

[i] Whilst it may seem odd that these devices have this additional layer of protection and not the higher risk devices, it is because the involvement of a notified body in the conformity assessment of Class I and custom-made devices is not required. Manufacturers self-certify compliance with the essential requirements for these devices, making the appropriate declaration regarding conformity, and affixing the CE marking to their devices before placing them on the market.

[ii] The Annexes describe how the rules contained in the Articles should be applied.

[iii] It shows the full text of the first six ERs, with key words highlighting the main focus of the requirement in bold text, and the main headings for the remainder. There are the mandatory safety requirements, briefly summarised briefly below, that manufacturers must comply with before affixing the CE marking to their device.

Table 9.4. Essential Requirements for medical devices

ER#	Essential Requirements (ER) Annex I, MDD (bold added)
ER1	The devices must be **designed and manufactured** in such a way that, **when used** under the conditions and **for the purposes intended**, they will **not compromise the clinical condition or the safety of patients**, or the safety and health of users or, where applicable, other persons, **provided that any risks** which may be associated with their use constitute **acceptable risks when weighed against the benefits** to the patient and are compatible with a high level of protection of health and safety.
ER2	The solutions adopted by the manufacturer for the design and construction of the devices must conform to **safety principles**, taking account of the generally acknowledged state of the art. In selecting the most appropriate solutions, the manufacturer must apply the following principles in the following order: - eliminate or reduce risks as far as possible (inherently safe design and construction), - where appropriate take adequate protection measures including alarms if necessary, in relation to risks that cannot be eliminated, - inform users of the residual risks due to any shortcomings of the protection measures adopted.
ER3	The devices must achieve the **performances** intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions referred to in Article 1(2)(a), as specified by the manufacturer.
ER4	The **characteristics and performances** referred to in Sections 1, 2 and 3 **must not be adversely affected to such a degree that** the **clinical conditions and safety** of the patients and, where applicable, of other persons **are compromised during the lifetime of the device** as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use.
ER5	The devices must be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will **not be adversely affected during transport and storage** taking account of the instructions and information provided by the manufacturer.
ER6	**Any undesirable side-effect must constitute an acceptable risk when weighed against the performances intended.**
ER7	Chemical, physical and biological properties
ER8	Infection and microbial contamination
ER9	Construction and environmental properties
ER10	Devices with a measuring function
ER11	Protection against radiation
ER12	Requirements for medical devices connected to or equipped with an energy source
ER13	Information supplied by the manufacturer

is only relevant to devices that have a measuring function, whilst ER11 is relevant solely to devices that emit radiation.

Devices must be designed and manufactured so as to not compromise patients' or others' health or safety when used as intended by the manufacturer, unless the risks are judged to be acceptable given the benefits to the patient and there is a high level of protection. All risks must be evaluated and managed during the design and construction of the device using a risk management process that seeks first to reduce risk by eliminating hazards where possible, then minimising them as far as possible, then providing alarms to warn of risks, and, finally, informing users of any residual risk, in that order. The specific risks to be addressed include those risks detailed more particularly in ERs 7-12, including risks related to or due to:

- contaminants and residues
- substances leaking from the device
- unintentional ingress of substances into the device
- infection or microbial contamination
- injury related to the device's physical features (volume/pressure ratio, dimensions, ergonomics)
- environmental conditions (setting) - magnetic fields, external electrical influences, electrostatic discharge, pressure, temperature, variations in pressure or acceleration
- reciprocal interference with other devices used in the treatment or diagnosis of patients
- ageing materials or loss of accuracy of measurement or control, where the device cannot be maintained or calibrated (e.g. implants)
- fire or explosion
- radiation
- electronic programmable systems (regarding repeatability, reliability and performance)
- dependence on an internal power supply
- electromagnetic fields that may be created by the device (that could interfere with other devices or equipment)
- electric shock
- mechanical features (e.g. resistance, stability, and moving parts)
- vibration
- noise
- terminals and connectors (to electricity, gas, hydraulic or pneumatic energy supplies)
- heat
- flows of energy or substances
- medicinal products or other substances delivered by the device
- medicines that are an integral component of the device
- disposal

Furthermore, the devices must perform as intended by the manufacturer; be designed, manufactured, and packaged to perform as intended; be able survive transport and storage (when the manufacturer's instructions are followed); and be able to withstand the stresses of normal use over its lifetime, all without adversely affecting the health and safety of patients. Unwanted effects must be acceptable when compared with the intended performances.

Instructions for use must be supplied so that the user can use the device safely and the device must be labelled, both of which must identify the device and any special precautions that must be taken, as well as details regarding sterilisation (if applicable), expiry date, handling/storage instructions, and any necessary warnings.

Declaration of Conformity & Conformity Assessment Procedures (Annexes II-VII)

These Annexes contain the CAPs available to medical device manufacturers. They are based on the conformity assessment modules described previously under Council Decision 90/683/EEC in section 10.3.1.2. Their correspondence to those modules is shown in Table 9.5. Annex II, V, and VI are EC Declarations of conformity that include inspection of their QMS by an NB, whereas Annex VII, which is also an EU Declaration of Conformity does not usually involve an NB unless the device has a measuring function or is intended to be sterile[i]. Annex III is an EC Type-examination in which a representation of the design process, such as a prototype, is examined for compliance with the technical documentation regarding its design. This design phase module must be combined with one of the production phase modules (i.e. Annexes IV, V, or VI) to complete the conformity assessment procedure. Article 11 specifies which of these is allowed based on the device's risk classification.

Table 9.5. MDD Annexes II-VI and their corresponding Modules in Council Decision 90/683/EEC

Annex	Module	Name	Phases covered	Verification of:
II	H	Full Quality Assurance	Design and Production	EC design examination and QMS for design, production, and final inspection & testing
III	B	EC Type-Examination	Design	Assess documentation and verify the type has been manufactured in conformity with the documentation
IV	F	EC Verification	Production	Examination and testing of all products (or a statistical sample of products)
V	D	Production Quality Assurance	Production	QMS for production and final Inspection & testing
VI	E	Product Quality Assurance	Production	QMS for final Inspection & testing

Statement concerning devices for special purposes (Annex VIII)

This refers to the statement required from manufacturers of custom-made or investigational devices. For investigational devices this involves drawing up a statement

[i] In other words, the manufacturer self-assesses their compliance with the ERs and any other legal requirements, but requires verification of compliance regarding the sterilisation process and/or any measuring function.

containing the following: a description of the device enabling its identification; the investigation plan, where it is being conducted, its start date and duration; the opinion of the research ethics committee (REC) regarding the investigation plan; the name of the clinician authorised to use the device and the institution responsible for the investigation; and a statement that the device conforms with the essential requirements except in respect to the aspects under investigation, and that everything has been done to protect the study participants from harm. Annex VIII also requires that additional documentation be kept available for the competent authorities that includes technical details and drawings on the device, the list of standards or other means used to meet the essential requirements, the risk analysis results, and the results of design calculations, inspection, and tests carried out. Furthermore, it mandates that the manufacturer ensures that the manufacturing process results in products that meet the design specifications set out in the technical documentation.

The requirements for statements to be made regarding custom-made devices are essentially the same as for investigational devices apart from the details relevant only to clinical investigations.

Classification Criteria (Annex IX)

This annex sets out the classification rues that determine which risk-class a device belongs in. There are eighteen classification rules (22 in the MDR, Annex VIII), which are based on the duration of contact with the body; the degree of invasiveness; whether it is reusable, requires an external energy source (active), its function (i.e. instrument, therapeutic, diagnostic), and what tissues it is in contact with. The rules are applied by assuming the device belongs to the highest-risk class and, taking its intended purpose to decide the answers, going through each of the rules asking whether it applies to the device (for its intended purpose) or not. For example, the classification is downgraded to Class I if it is: non-invasive (Rule 1); not in contact with critical tissues (i.e. blood, cardiovascular or nervous systems)(Rule 2); doesn't modify the composition of the blood or other body fluids (Rule 3); acts as a mechanical barrier for injured skin (not breaching the dermis or altering the micro-environment) (Rule 4); is only transiently invasive (i.e. not in contact with the body for more than 60 minutes (Rule 5); doesn't incorporate medicines or human blood derivatives (Rule 13). If any of these is not the case however, the device belongs in a higher risk class.

Invasive, implantable, and active implantable devices have additional rules that may allow them to be down-classified depending on their intended use. These include if the duration of contact is only short-term; invasiveness is limited to certain natural body

orifices/cavities and the device remains unabsorbed; connection to an active device is not required; it is used for disinfecting surfaces or non-invasive devices; or is intended for recording x-ray diagnostic images.

For the most part, the following devices remain in Class III (though some may be downgraded as explained above):

- implantable devices, including implantable contraceptive devices
- devices incorporating medicine or human blood derivatives
- devices manufactured using animal tissues (or derivatives rendered non-viable)
- devices in direct contact with the cardiovascular or central nervous systems
- devices directly contacting either of the cardiovascular or central nervous systems that is used to control, diagnose, monitor, or correct a defect in one of them
- devices that are intended to be used in direct contact with the heart or the central circulatory or nervous systems
- devices with a biological effect or that are bioabsorbable
- devices that are intended to undergo a chemical change in the body

For the most part, active non-implantable devices, including those emitting ionizing radiation, belong in Class IIa or IIb.

Clinical evaluation (Annex X)

This sets out requirements for the clinical evaluation of medical devices referred to in Annex I, which states that '*Where conformity with the essential requirements must be based on clinical data, as in Section I (6)*[i]*, such data must be established in accordance with Annex X*.[1, Annex I (14)] Section I(6) states: 'Any undesirable side-effect must constitute an acceptable risk when weighed against the performances intended.'[1, Annex I (6)]

Therefore, clinical data is required for determining if the profile and rate of AMDEs is considered acceptable by the manufacturer when compared with the anticipated clinical benefit as claimed by the manufacturer. The MDD does not specify a requirement to demonstrate the clinical efficacy or effectiveness of the device.

The requirement for clinical data is probably the single biggest difference between the MDDs and the other New Approach Directives.

However, this clinical data may be derived from:

[i] 'Any undesirable side-effect must constitute an acceptable risk when weighed against the performances intended'.

'*1.1.1. either a compilation of the relevant scientific literature currently available on the intended purpose of the device and the techniques employed as well as, if appropriate, a written report containing a critical evaluation of this compilation; 1.1.2. or the results of all the clinical investigations made, including those carried out in conformity with Section 2.*'[1, Annex X (1)]

Furthermore, '*All the data must remain confidential,*'[1, Annex X (1)]

This means that clinical data, which may be derived from the literature, is needed to assess the

Section 2 sets out the requirements for clinical investigations, including its objectives, ethical consideration, and methods. The objectives of the clinical investigation are not to assess clinical effectiveness, but '*to verify that, under normal conditions of use, the performance of the devices conform to those referred to in Section 3 of Annex I*[i]*, and* '*to determine any undesirable side-effects, under normal conditions of use, and assess whether they constitute risks when weighed against the intended performance of the device.*'[1, Annex X (2)] Therefore, clinical data is required for determining if the risk of AMDEs is acceptable given the expected intended performance of the device. However, there is no legal requirement to assess actual clinical outcomes from the device.

Clinical investigations, where they are conducted, are required to comply with the ethical principles contained in the Declaration of Helsinki, which includes the publication of the study's results. However, the only mechanism provided for checking this and preventing unethical studies from being conducted is via the REC's ethical review, whose only power to prevent trials with unethical investigation plans is by issuing a negative opinion.

No specific research methods are provided, instead the methods must: follow '*an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute the manufacturer's claims for the device; these investigations must include an adequate number of observations to guarantee the scientific validity of the conclusions.*'[1, Annex X (2)]; be appropriate for the device; conducted in similar conditions to usual practice; investigate the safety, performance, and effects on the patient; record and report all AMDEs; and be performed by or under the supervision/responsibility of a suitably qualified clinician, who must have access to the data (clinical and technical) and prepare a written report on the evidence on conclusion of the investigation. There are no other requirements. Specifically, there

[i] i.e. the device must '*achieve the performances intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions referred to in Article 1(2)(a)*[i]*, as specified by the manufacturer*'[1, Annex I (3)]

is no requirement to utilise an RCT design, minimising bias and confounding, to assess clinical efficacy.

This means that the manufacturer decides what the intended purpose of the device is, its intended performances, what the risks are, whether they're are acceptable, and whether to conduct a clinical investigation (and if so, the study design) or rely on evidence from the literature to demonstrate conformity and obtain CE marking.

Criteria to be met for the designation of notified bodies (Annex XI)

This annex sets out the requirements for designating notified bodies. These include:

- staff are not involved in the design or production or any other part of the supply chain for the device(s) that they are assessing
- staff must be competent carrying out assessments and verifications, work with integrity, and be free from all pressures/inducements, particularly from vested interests
- the NB must be able to carry out the tasks it is designated for, have the necessary resources (staff, facilities, and testing equipment), knowledge, and skill to conduct its tasks and/or have responsibility for any specific subcontracted tasks
- the NB must have a training programme for their staff, have satisfactory knowledge of the rules on inspections and adequate experience, and be able to draw up certificates and the records and reports on the inspections
- Impartiality must be guaranteed
- the NB must have civil liability insurance (unless indemnified by the MS)
- staff are bound to secrecy of all information obtained in the course of their work, except where disclosure is legally required
- subcontractors must be required to fulfil the requirements of the Directive, especially those in this Annex

CE Marking (Annex XII)

This Annex simply provides details on the appearance and dimensions of the CE conformity marking.

9.3.2. Amendments to the MDD

The MDD was amended by the legislation listed in Box 9.5. Some of the amendments that these introduced included changes in definitions and scope (e.g. to include blood products and medicinal substances incorporated as an integral part of the device, but with an action that is ancillary to that of the device); changes to the committee on standards and technical regulations; and additional clauses, such as rules on

reprocessing, the establishment of a European databank (the forerunner of EUDAMED), and the introduction of cooperation between the NCAs (sharing experience and information), amongst others. They did not, however, change the principal approach adopted for regulating medical devices from that proposed in the EEC's New Approach policy. The MDD was subsequently replaced in 2017 by the MDR, which is detailed in the next section.

How the rules are applied is the subject of the next chapter.

9.4. The revised legal framework

The revised legal framework consists of the MDR, IVDR, and any subsequent corrigenda or amendments, and any implementing or delegated acts based on the MDR or IVDR.

This section focusses on the MDR, providing a brief description of its rules, comparing them with the main rules in the MDD, and specifically exploring the changes it introduces, pointing out changes that it doesn't make, and how this impacts medical device safety and evidence availability for assessing a device's safety and efficacy/effectiveness. Corrigenda, amending, delegated, and implementing legislation for the MDR is listed in Appendix 14.11.

9.4.1. Overview of the Medical Device Regulation (MDR), 2017

The MDR contains 101 recitals, ten chapters, containing a total of 203 Articles, and seventeen Annexes. Contrasting with the MDD, it provides 71 definitions of terms.

As can be seen from Table 9.6, which provides a summary overview of the chapters (containing the Articles) and the Annexes in the MDR, it follows a similar pattern to the New Approach directives, containing: the scope (Chapter I); a general clause for placing on the market (Chapter II); essential requirements (Annex I); a free movement clause (Chapter I); means of proof of conformity and effects (Chapter V and Annexes IX-XI); and means of attestation of conformity[i] (Chapter II and IV; Annexes IV-V). Not so obvious from the summary table is the fact that the MDR also provides for a standing committee, and its tasks and operational procedures, in Article 114, Chapter X; safeguard actions in Articles 94-96, Chapter VII similar to the New Approach safeguard clause; and the use and management of a list of harmonised standards in Article 8, Chapter II. In other words, it adopts all the elements of the New Approach.

Enacted in accordance with the NLF,[410] the MDR follows the pattern set out in the NLF, which is essentially the same as the New Approach, but with tightened definitions of the

[i] This includes CE marking (Article 2, Chapter II; Annex V), including the notification of notified bodies (Chapter IV), and the manufacturer's declaration of conformity (Article 19, Chapter II; Annexes IV).

Table 9.6. List of contents of the MDR

MDR: Table of Contents		Articles	Page
Chapter			
Chapter I	Scope and definitions	1-4	13
Chapter II	Making available on the market and putting into service of devices, Obligations of economic operators, Reprocessing, CE marking, Free movement	5-24	21
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	25-34	34
Chapter IV	Notified bodies	35-50	40
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Chapter VI	Clinical evaluation and Clinical investigations	61-82	55
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Chapter VIII	Cooperation between member states, Medical Device Coordination Group, Expert laboratories, Expert panels and Device registers	101-108	82
Chapter IX	Confidentiality, Data protection, Funding and Penalties	109-113	86
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Annexes			
Annex I	General safety and performance requirements		94
Annex II	Technical documentation		108
Annex III	Technical documentation on post-market surveillance		112
Annex IV	EU declaration of conformity		113
Annex V	CE marking of conformity		114
Annex VI	Information to be submitted upon the registration of devices and of 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		115
Annex VII	Requirements to be met by notified bodies		123
Annex VIII	Classification rules		140
Annex IX	Conformity assessment based on a quality management system and on assessment of technical documentation		146
Annex X	Conformity assessment based on type-examination		155
Annex XI	Conformity assessment based on product conformity verification		157
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actors involved (economic operators and regulators) that clarify to whom the responsibilities imposed by the MDR are assigned, and the requirement for mutual recognition of accreditation bodies and their decisions. It establishes a system of conformity assessment, but similar to the MDD, it also adopts additional requirements, such as classifying devices according to their risks, assigning the CAPs allowable according to risk class, and requiring clinical data (through clinical evaluation, sometimes including clinical investigation) to demonstrate certain of the essential requirements.

9.4.1.1. General safety and performance requirements

The MDR sets out the essential requirements as general safety and performance requirements (GSPRs) in Annex I, which are the maximum requirements that MS may impose on medical devices, mandating MS to allow the free movement of devices carrying the CE marking (Article 24). Again, the CE marking indicates compliance with the legal requirements, and the MDR does not replace this with a centralised pre-market approval or authorisation process, even for high-risk devices. To be allowed to place the CE marking on their devices, manufacturers must meet the GSPRs and any other relevant legal requirements (such as those in the machinery directive, if relevant), perform a conformity assessment procedure, which may involve verification by an NB of their choosing, and make a written declaration of conformity containing the information listed in Annex IV. This information includes details identifying the manufacturer, the device (including its risk class and UDI-DI), the assessing NB, the common specifications (CS) applied (if any), and the signatory of the DoC, together with statements declaring that the device conforms with the MDR (and any other legal requirements) and assuming responsibility for the DoC.

There are twenty-three GSPRs detailed in Annex I, including thirteen that detail specific hazards that must be avoided, minimised, or have controls/alarms applied, and inform users of their residual risks (points 10-22). Similar to the MDD, manufacturers must apply a risk management system (points 2-5); devices are required to not deteriorate to such an extent that it affects their intended performance during normal use (point 6) or during transport or storage (point 7); the side effects experienced must be considered to be an acceptable risk given the device's intended performance (point 8); and the final GSPR details the information that must be supplied with and/or on the device (point 23). Additionally, the scope of the MDR is extended to apply to specific categories of product that are not intended for medical purposes, but which carry similar risks to similar devices that are intended for medical purposes. Consequently, one of the GSPRs addresses this, requiring that such products (listed in Annex XVI), must not present unacceptable risks

to users (point 9). The biggest difference in the GSPR as compared with the ERs in the MDD is that the first GSPR requires that devices are safe and effective, as well as performing as intended and not compromising the clinical condition or safety of patients unless the risks are considered acceptable when compared with the anticipated benefits. This is the only mention in the MDR that devices must be effective. Furthermore, despite being a GSPR, none of the Annexes detailing the CAPs make any demands for evidence of effectiveness, all refer instead to the requirement that devices perform as intended.

9.4.1.2. Conformity Assessment Procedures

There are three Annexes providing CAPs, Annexes IX-XI. The first of these is based on the assessment of the manufacturer's quality management system and their technical documentation, the second is based on type-examination, and the third is based on product conformity verification. Hence, Annex IX of the MDR is similar in nature to the full quality assurance CAP detailed in Annex II of the MDD; Annex X is similar to the EC Type-Examination in Annex III of the MDD; and Part A of Annex XI is similar to the Production quality assurance in Annex V of the MDD, whilst Part B is similar to the Product quality assurance in Annex VI of the MDD. The difference between the two lies in the amount of detail specified in the MDR compared with the MDD. According to Article 52 Class III implantable devices must undergo a CAP applying all sections of Annex IX or all sections of both Annex X and XI.

The technical documentation to be included by manufacturers in their applications to have their QMS/technical documentation assessed is specified in far greater detail than in the MDD. However, the details are very similar to the contents of the GHTF guidance summarising the technical documentation that they recommend including to demonstrate compliance with the 'essential principles', which is essentially the same concept as the 'essential requirements'.[422] So, manufacturers complying with the GHTF guidance would largely already be compliant with the technical documentation requirements of the MDR. The concept of equivalence between devices that allows the clinical evaluation to be based on evidence from the literature on a predicate device remains, but equivalence has now been defined (which was not the case in the MDD). Devices are only equivalent, and therefore, can only be used to provide predicate evidence, if they are similar technically, biologically, and clinically, so that they essentially are constructed of the same/similar materials, have a similar biological effect/reaction in the body, are used in a similar body location in a similar manner, and have a similar clinical indication with similar benefits and risks.[3 Annex XIV(3)] Furthermore, manufacturers must have access to

the data supporting the predicate device, requiring a contract with another manufacturer to agree access to the data if the predicate belongs to another manufacturer

Similarly more details are required to be included in the clinical evaluation and the PMS. However, both still concentrate on acquiring evidence related to risks and safety, and to a lesser extent evidence on device performance and benefits (rather than efficacy).

9.4.1.1. Changes introduced to improve patient safety

The MDR has introduced several changes that have the potential to improve patient safety. This section describes some of these.

The MDR requires that manufacturers create a summary of the safety and clinical performance of their device (SSCP) (Box 9.6) for implantable and Class III devices (that are not custom-made or investigational devices), which is to be kept up-to-date, and which is to provide a summary of the evidence upon which the CE marking is based. The clinical information that it is to contain includes a summary of the clinical evaluation, any relevant PMCF information, and possible diagnostic or therapeutic alternatives.

Historically, the evidence upon which a device has been allowed onto the market is confidential, but with the introduction of the requirement for this SSCP to be uploaded to the European databank for medical devices, EUDAMED, and made publicly available when this functionality has been developed[i], there is the hope that some of the clinical evidence will be made available. However, this functionality (module) has not yet been developed, so it remains to be seen how much detail will become available and whether it will have clinical utility.

Article 32 (2)

(a) the **identification** of the **device** and the **manufacturer**, including the Basic UDI-DI and, if already issued, the **SRN**;

(b) the **intended purpose** of the device and any indications, **contraindications** and **target populations**;

(c) a **description of the device**, including a reference to **previous generation(s) or variants** if such exist, and a **description of the differences**, as well as, where relevant, a **description of any accessories, other devices and products**, which are **intended to be used in combination with the device**;

(d) possible **diagnostic or therapeutic alternatives**;

(e) **reference to any harmonised standards and CS applied**;

(f) the **summary of clinical evaluation** as referred to in Annex XIV, and **relevant** information on **post-market clinical follow-up**;

(g) **suggested profile and training for users**;

(h) information on any **residual risks** and any **undesirable effects**, **warnings** and **precautions**.

Box 9.6. Contents of the summary of safety and clinical performance (bold added)

[i] In the meantime manufacturers are obliged to make the SSCP available on request to

The MDR also places greater requirements on manufacturers regarding post-market safety. It requires that manufacturers put a plan in place for PMS, have structured process for conducting PMS, and a post-market clinical follow-up (PMCF) plan to identify what evidence is not yet available and to develop plans to generate that evidence. However, in some instances manufacturers are instead allowed to justify why they do not have PMCF plan,[3 Annex II(6.1)(d)] which means that this requirement can be avoided.

EUDAMED, which will be described in more detail later, improves coordination of activities between the CAs, particularly regarding vigilance and market surveillance, enabling them to more speedily detect devices causing or potentially serious harm and to ask manufacturers to take corrective and/or preventive actions (CAPA). The MDR also gives more power to the CAs to demand that manufacturers act on their requests by empowering them to restrict, withdraw, prohibit, or recall the device from the market until the manufacturer cooperates/provides the necessary information.[3 Article 10(14)(2nd para)] EUDAMED also provides the CAs and the DAs with greater oversight of their NBs activities and certificates.

For Class III implantable devices and Class IIb devices intended to administer/remove medicines[i], NBs must apply for a clinical evaluation consultation procedure (CECP), where an expert panel reviews their assessment of the manufacturer's clinical evaluation. The application for a CECP must also include their clinical evaluation assessment report detailing their conclusions regarding the clinical evidence provided by the manufacturer, especially related to the benefit-risk determination, and the evidence's compatibility with the intended purpose, clinical indication and the manufacturer's PMCF plan.[3 Annex VII(5.1)(a)] The NB, may however, decide differently to the opinion issued from the CECP, but must justify their decision. All such instances must also be recorded in the Commission's annual overview of the CECP that is presented to the Council, EP, and the MDCG.

Manufacturers of implantable devices and Class III devices are also required to prepare a periodic safety update report (PSUR) annually as part of their PMS plan. Their PSURs are to be included in their technical documentation, and for Class III or implantable devices these PSURs must also be uploaded to EUDAMED and evaluated by the relevant NB, who then add an evaluation report to EUDAMED.[3 Article 86] These are made available to the CAs and the Commission, which should improve their oversight.

[i] With certain exceptions – where the certificate is a renewal, where the device is a modification of a previous one by the same manufacturer with the same purpose and has demonstrated no ill effects to the benefit-risk balance,, or where there are CS covering the aspects for clinical evaluation that the manufacturer has appropriately applied.

However, no requirement is made to make them publicly available, instead the public and healthcare professionals will be given access to vigilance and PMS data at an unspecified 'appropriate level'.[3 Article 92(3)] Nevertheless, this was the first time that manufacturers had to send regular reports to the notified bodies, which makes it possible for them to monitor the safety of the devices they have to some extent responsibility for. The exchange of information related to post-market surveillance and PSURs via EUDAMED is not yet mandatory, as EUDAMED is not yet fully functional, so the previous arrangements for information exchange between MS, NBs and the Commission remain as they were under the MDD until then.[3 Article 123]

Article 91 empowers the Commission to enact implementing acts to provide the necessary arrangements and procedures involved in conducting post-market surveillance, including aspects related to the PSURs, trend reports, and periodic summary reports[i].

In addition to the HS described previously, whose use confers a presumption of conformity with the relevant applicable ER/GSPR, the MDR empowers the Commission to adopt implementing acts to adopt common specification (CS), These are technical or clinical requirements not contained in a standard, but that provide an alternative means of compliance with a specific requirement,[3 Article 1(71)] the use of which confers a presumption of conformity with the relevant provision/requirement. The advantage of their being established through an implementing act means that the details contained in the CS should be publicly available, unlike the HS, which exist behind a paywall and are subject to confidentiality requirements. The CS concentrate on requiring manufacturers to adopt a RMS, detailing more specific risks relevant to the particular group of products that they must take into account, and specifying the labelling and IFU requirements.

Compared with the MDD, the scope of the regulation of products has been extended by MDR to cover devices that don't have an intended medical purpose themselves but are similar to regulated medical devices. The types of device that fall into this category, which must comply with the MDR, are listed in Annex XVI. The Commission is also empowered to make changes to this list through delegated acts.[3 Article 1(5)] This was a significant gap in the MDD, as it was possible for manufacturers to evade having to conform to the MDD if they could declare it to not have a medical purpose, yet the associated risks could still be significant.

[i] Periodic summary reports may replace serious incident reports for the same or similar device types in cases where there are similar incidents with an identified cause or if FSCAs have been implemented or the incidents are common and well documented, and where the CA has agreed on the format, content, and frequency of reporting

9.5. Discussion

The dizzying array of institutions involved in the enactment of EU legislation, the variety of legislative procedures, and their complexity, makes it difficult for interested individuals to understand the legislative process, and therefore makes it difficult for them to exert any influence on it. In fact, to do so, they need to have the time, and other resources necessary to acquire this knowledge, which effectively precludes individuals or small interest groups from the policy-making process, supporting Stigler's assertion that '*the political system does not offer good incentives like those in private markets to the acquisition of knowledge*.[145, p.11]

The composition of the institutions and the specific committees/working groups involved in enacting the MDD structurally favour the advancement of economic and trade goals over healthcare goals. In addition to the theme of authority and power, one of the key themes which is evident in these documents is the focus on reducing barriers to trade, strengthening the internal market, and increasing its size. The 'New Approach' directives were an extension of that. Their focus, and intention, was to enhance trade by removing the technical barriers to trade, and thus establishing the 'internal market' envisaged by the treaties.

The MDD was just one of a suite of directives enacted under the 'New Approach', which meant that the main thrust of the directives was generic rather than specific to a particular kind of product. This is significant as it meant that there was little focus on regulating for patient safety or for ensuring the clinical effectiveness of devices – these were either assumed or left to market forces to achieve. The treaties go into a lot of detail on quotas, and budgetary matters, but also on the rights and responsibilities of MS and the role of the EU institutions to implement and enforce these. Healthcare is left to the MS to organise and fund, therefore, patients and healthcare outcomes were not a key consideration in the drafting and enacting of the MDD (and arguably, this still holds true for the MDR).

Another theme that emerged is complexity, resulting from the constant change. The institutions have changed, the number of MS has grown (and subsequently decreased with Brexit), the legislative procedures have changed, and everything has become more complex. Starting with just six MS with four languages, there are now 27 MS with 24 official languages, requiring all official documents to be translated into all 24 languages (with some exceptions for Irish), including technical and legal linguistic terms. The changes and complexity make it difficult to ascertain what exactly happened when. Although there is an increasing focus on transparency and making documents available

to the public, many of the older ones are not readily available in English or are difficult to find. Furthermore, minutes of committee meetings and trilogues are mostly not available or lack detail. The lack of transparency obscures the motivation underpinning the legislation, notably market liberalisation. The public may assume that the purpose of the legal framework for medical devices is to ensure that only safe and effective devices are allowed to enter the EU healthcare systems[i]. However, this was not their purpose. They were intended to remove barriers to trade caused by varying safety requirements across MS (whilst, in theory, maintaining or improving the level of safety required by each). Thus, safety requirements were the cause rather than the goal of the MDD.

In fact, one of the main goals of the New Approach directives was to instil confidence in CE marking, thereby ensuring the acceptability of such products by MS that had stricter controls, particularly regarding the safety of products entering their home markets.[383]

In this regard the New Approach has succeeded, not only in removing barriers to trade, but also in engendering trust in the CE marking. The New Approach also meant that individual nations were stripped of their power to enact more stringent legislation, except in the case of protecting workers – another key objective of the treaties. This was legally justified on the basis that the CE marking indicated that the 'essential requirements' had been met with regard to product safety. However, as product safety is generally conceptualised as harm arising from the use of the product, this means that the focus is on the safety of the user (which in the case of implantable devices are the surgeons), and not specifically on patients.[423] Conceptualising safety in terms of harms arising from the use of a device fails to take into account either the need for clinical effectiveness or the fact that the device shouldn't be less effective than the alternative treatments available, at least not without providing some other clinically important benefit.

The New Approach also made it impossible for the necessary evidence to be made available to clinicians, their patients, or the public by imposing confidentiality clauses on all the actors involved in the regulatory process, regarding any information they receive in the course of their work. This means that even when regulators become aware of the limited evidence for efficacy or of evidence suggesting that a device may not be safe in some people or under particular conditions, they cannot disclose this, unless it is first made known by the manufacturer or the relevant economic operator.

[i] Assuming that regulating market entry determines what reaches the healthcare system.

10. Implementation and effects on evidence and safety

How are medical devices regulated? And how does this affect patient safety?

For any legal framework to achieve its goals it is necessary to establish an effective system for implementation and enforcement. This requires that necessary structures and processes to be put in place and resources be made available to enable them to function as intended.

The objective of this chapter is to explore the implementation process for the EU's legal framework(s) for medical devices, its outcome or effects on patient safety and the availability of evidence to evaluate patients' outcomes.

The arrangements for implementing the medical device legal framework(s) are complex and relatively obscure. The system involves a complex web of actors, with NBs who assess the conformity of a device; national accreditation bodies that accredit them (to certify that they meet certain required standards for conducting a conformity assessment procedure); designating authorities that give NBs the authority to perform conformity assessments; and competent authorities that authorise clinical investigations and perform market surveillance for medical devices.

For each of these there is also a higher level association that represents their members, providing guidance for performing their tasks or relevant reports. Additionally, there are the standards organisations, both European (ESOs) and national, involved in harmonising standards and selling them.

The involvement of all these varied actors makes the implementation of the EU's regulatory framework complex. This chapter provides an overview of these actors, with a brief description of the most relevant processes involved in implementing the MDD and the changes in these introduced by the MDR, followed by a discussion on the National Competent Authority Reports (NCARs) and the limited evidence that they provide regarding patients' outcomes following the implementation of first the MDD, and later the MDR in Section 10.3.

10.1. Implementation Structures

This section describes the key actors involved in the implementation and, to a lesser extent, the enforcement of the MDDs and MDRs. Figure 10.1 demonstrates the complex network of regulatory actors involved., with those in white boxes being more directly involved, and those in grey (most of which are umbrella bodies for the relevant actor group) being involved more peripherally. The national standards bodies are in grey, because they take less of a role than the ESOs in determining the contents of the standards, at least in theory.

Each of the actor groups is described in this section, with legal definitions provided in the Glossary and in Table 10.2, which provides a summary of the regulatory authorities in Ireland, defining the tasks entrusted to them. Table 10.1 summarises the numbers and types of actors involved in implementing the MDD/MDR across Europe.

Table 10.1. Actors and stakeholders involved in the regulation of medical devices

Actor/Stakeholder	Number	Source
Member States (MS)	27	
European Economic Area nations	30	
Accreditation Bodies(ABs)	28	EU Commission[i]
Designating Authorities (DAs)	39	EU Commission[ii]
Notified bodies (NBs)	57	EU Commission[iii]
Competent Authorities (CAs)	67	EUDAMED[iv]
Manufacturer (includes 893 Systems/Procedure Pack Producers)[v]	22,614	EUDAMED[vi]
Authorised Representative (Supplier)	2,062	EUDAMED[vii]
Importer	6,577	EUDAMED[viii]

10.1.1. Designating (Notifying) Authorities

Designating or Notifying Authorities (DAs) are the national bodies designated by individual MS as competent and responsible for assessing any organisations applying to become a CAB under one of the New Approach Directives. They are responsible for notifying the Commission when it has approved a CAB as a notified body and for monitoring its compliance with the legal requirements placed on NBs under the relevant legislation (e.g. the MDD).

[i] https://webgate.ec.europa.eu/single-market-compliance-space/#/notified-bodies/notified-body-list?filter=legislationId:13,notificationStatusId:1
[ii] https://webgate.ec.europa.eu/single-market-compliance-space/#/notified-bodies/notifying-authorities?filter=legislationId:13
[iii] https://webgate.ec.europa.eu/single-market-compliance-space/#/notified-bodies/acred-bodies
[iv] https://ec.europa.eu/tools/eudamed/#/screen/competent-authorities?submitted=true
[v] https://ec.europa.eu/tools/eudamed/#/screen/search-eo?actorTypeCode=refdata.actor-type.system-procedure-pack-producer&submitted=true
[vi] https://ec.europa.eu/tools/eudamed/#/screen/search-eo?actorTypeCode=refdata.actor-type.manufacturer&submitted=true
[vii] https://ec.europa.eu/tools/eudamed/#/screen/search-eo?actorTypeCode=refdata.actor-type.authorised-representative&submitted=true
[viii] https://ec.europa.eu/tools/eudamed/#/screen/search-eo?actorTypeCode=refdata.actor-type.importer&submitted=true

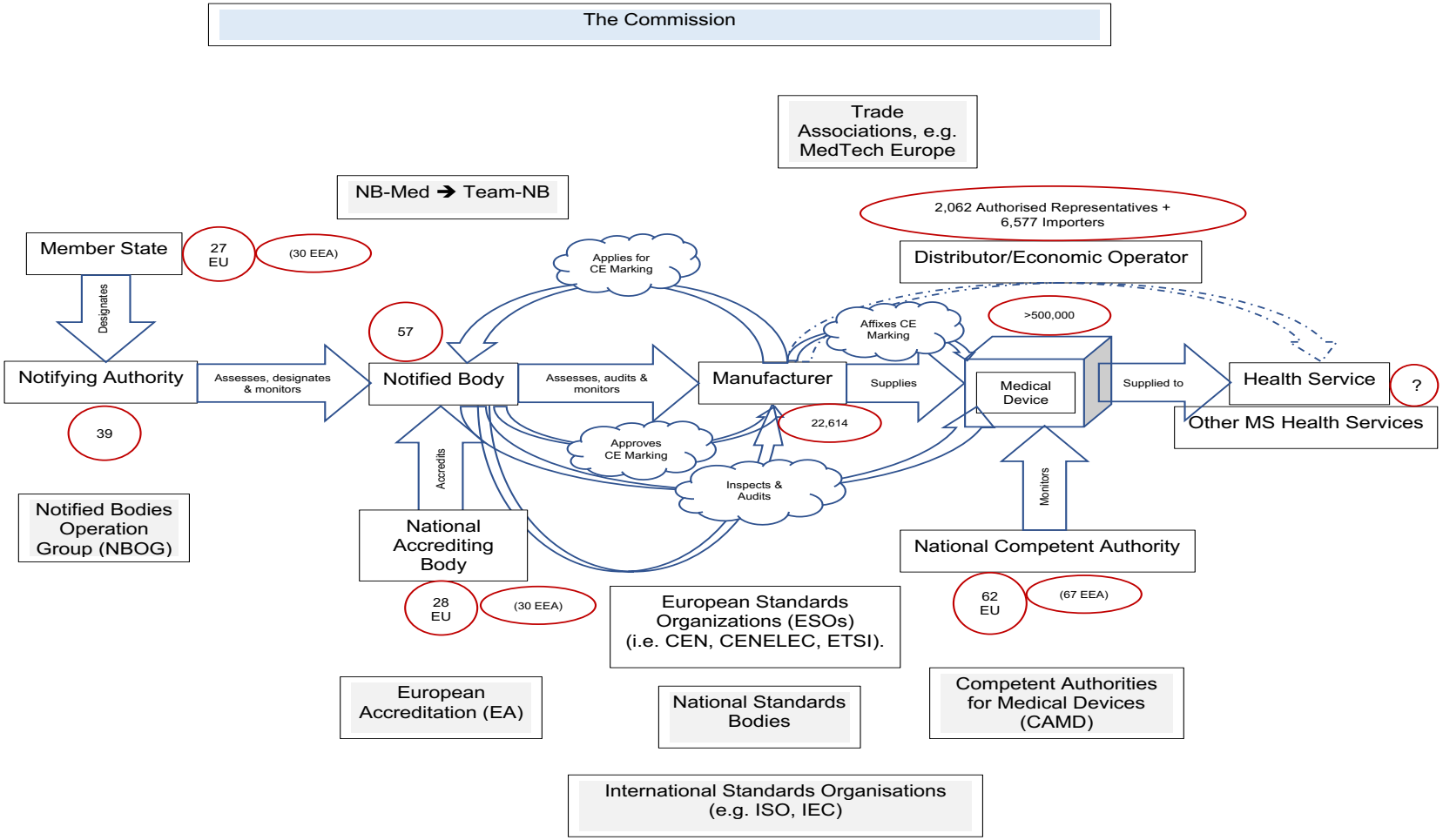

Figure 10.1. Actors involved in regulating medical devices in the EU (the numbers are only indicative as they are subject to change)

Table 10.2. Summary of the Irish regulatory bodies involved with medical devices

Body	Activity	Definition	Irish Representative Body
Designating Authority (also called Notifying Authority)	Regulates and Notifies organisations as authorised to perform conformity assessment of products under a specific EU Directive(s)	Notification is an act whereby a Member State informs the Commission and the other Member States that a body, which fulfils the relevant requirements, has been designated to carry out conformity assessment according to a directive. Notification of Notified Bodies and their withdrawal are the responsibility of the notifying Member State.[424]	Health Products Regulatory Authority (HPRA) is the Notifying Authority in Ireland
Competent Authority (CA)	Market surveillance and/or of vigilance for devices	'Market Surveillance' means the activities carried out and measures taken by competent authorities to check and ensure that devices comply with the requirements set out in the relevant Union harmonisation legislation and do not endanger health, safety or any other aspect of public interest protection.[3, Article 2, para 61] The vigilance system is the name given to the process of notification and evaluation of specific types of incidents that are shared between the national CAs and the European Commission.[425]	HPRA is the CA in Ireland under Directive 93/42/EEC Medical devices Department of Agriculture, Food and the Marine (DAFM) is the CA in Ireland under Regulation (EU) No. 528/2012.
Notified Body (NB)	Conformity Assessment	Conformity Assessment is the 'systematic examination of evidence generated and procedures undertaken by the manufacturer, under requirements established by the Regulatory Authority, to determine that a medical device is safe and performs as intended by the manufacturer and, therefore, conforms to the Essential Principles of Safety and Performance for Medical Devices.'[426]	National Standards Authority of Ireland (NSAI) is the NB in Ireland for Medical devices
The European cooperation for Accreditation (EA) & the National Accreditation Bodies	Accreditation	'Accreditation' means an attestation by a National Accreditation Body that a Conformity Assessment Body meets the requirements set by harmonized standards and, where applicable, any additional requirements including those set out in relevant sectoral schemes, to carry out a specific conformity assessment activity.[427]	Irish National Accreditation Board (INAB)
National Standards Organisation	Supplies harmonised standards	National authority designated for approving national technical specifications and regulations laying down the characteristics required of a product such as levels of quality, performance, safety or dimensions.[428]	NSAI

As of September 2023, there were thirty-nine DAs across all MDDs/MDRs, thirty-six from MS, one from the Commission itself, and six from non-EU countries (Australia, Turkey,

Iceland, New Zealand, Norway, and Switzerland)[i]. Australia doesn't yet have a DA for the MDR/IVDR, nor does New Zealand. Norway doesn't have one for the IVDMDD and Turkey doesn't yet have one for the IVDR. The designation as a DA under the MDDs has moved to a different organisation under one or both of the MDRs in five MS (Austria, Belgium, Malta, Poland, and Sweden) each of which moved to an organisation more suited or with more experience in healthcare products.[ii]

As of August 2021, there were thirty-nine DAs with thirty-three DAs covering the MDR/IVDR listed on the NANDO website (34 for the AIMDD, 35 for the MDD, and 35 for the IVDMDD). All were DAs for the MDR, only one, from Turkey, is not designated as DA for the IVDR. Whilst this sounds confusing, it demonstrates the complexity of both the regulatory structures and the difficulty in identifying who holds the relevant information governing the NBs and the quality of their conformity assessment reviews.

In some MS, the same organisation is tasked with performing market surveillance, (i.e. they are the national competent authority (CA)) and performing the notification of CABs, which is the role of the DA, but this is not always the case. In fact, in 2021, twelve of the MS had designated the same body as DAs and CAs under both the MDDs and the MDRs, twelve had separate bodies for these functions, whilst three others had separate bodies under the MDDs, but changed to a single body under the MDR, with the CAs also becoming the DAs. The significance of this is that due to confidentiality requirements DAs and CAs cannot share information except in the case of suspicion that there is a medical device with a significant risk of causing severe AMDEs. However, where the CA is also the DA responsible for designating the NB(s) in their jurisdiction they have more information about the NB, its work practices, and its method of data collection. Furthermore, they can inspect premises and documentation if they suspect a problem with the NB, which gives them better access to data relevant to safety.

In Ireland, the Health Products Regulatory Authority (HPRA) is both the DA and the CA.

10.1.2. National Accreditation Bodies

Each member state, EEA countries, and other affiliated countries designates a single national accreditation body, authorised to assess the competency of CABs in one or more of the following:

[i] [Internet]. Accessed 2023 Sep 21. Available from: https://webgate.ec.europa.eu/single-market-compliance-space/#/notified-bodies/notifying-authorities?filter=legislationId:13
Although this depends on the source. EUDAMED lists just 27 Actors as Designating Authorities. It is possible that this is because the others haven't registered in EUDAMED, or EUDAMED may only be for the use of EU MS, or it may be that they haven't been delisted from the Commission's website yet.

[ii] Data collated from the NANDO website, available here: https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=na.main

- Calibration,
- Testing
- Medical Examination
- Product Certification
- Management Systems Certification
- Certification of Persons
- Inspection
- Validation and Verification
- Proficiency Testing Providers
- Reference Material Producers.

Based on Regulation (EC) No 765/2008, DAs may, but are not obliged to, rely on the accreditation body's assessment of competency when they make their decision to notify a notified body.[407] The HPRA does not rely on the Irish National Accreditation Body (INAB) to assess the competence of the National Standards Authority of Ireland (NSAI), which is both the NB for medical devices in Ireland and the national standards authority[i]. However, not all MS choose to do this, but regardless of whether the DA relies on accreditation or assesses a CAB's competency themselves, their decision regarding notification must be recognised by all MS.

10.1.3. Notified Bodies

NBs are designated to perform a conformity assessment according to the requirements of specific EU legislation (such as particular Directives or Regulations). Following the DAs evaluation of a successful applicant for the role of conformity assessment, the DA informs the European Commission and the other MS, through a process of 'notification', that the applicant is now an NB under that Directive/Regulation, and that it fulfils the relevant requirements within a specified scope of practice.

All designated NBs are listed on the NANDO website (New Approach Notified and Designated Organisations information system[ii]), including their scope, identification number, and contact details, under the relevant legislation.[424] This notification procedure is available to all EU MS and any other jurisdiction with which the EU has established treaties, agreements or protocols that allow them to avail of the procedure. For example, the European Free Trade Association (EFTA) or the European Economic Area (EEA) countries and signatories of the Mutual Recognition Agreements (MRAs) and Protocols to the European Agreements on Conformity Assessment and Acceptance of Industrial Products (PECAs).[424]

[i] However, the NSAI has been accredited for other competencies by INAB.
[ii] https://webgate.ec.europa.eu/single-market-compliance-space/#/notified-bodies

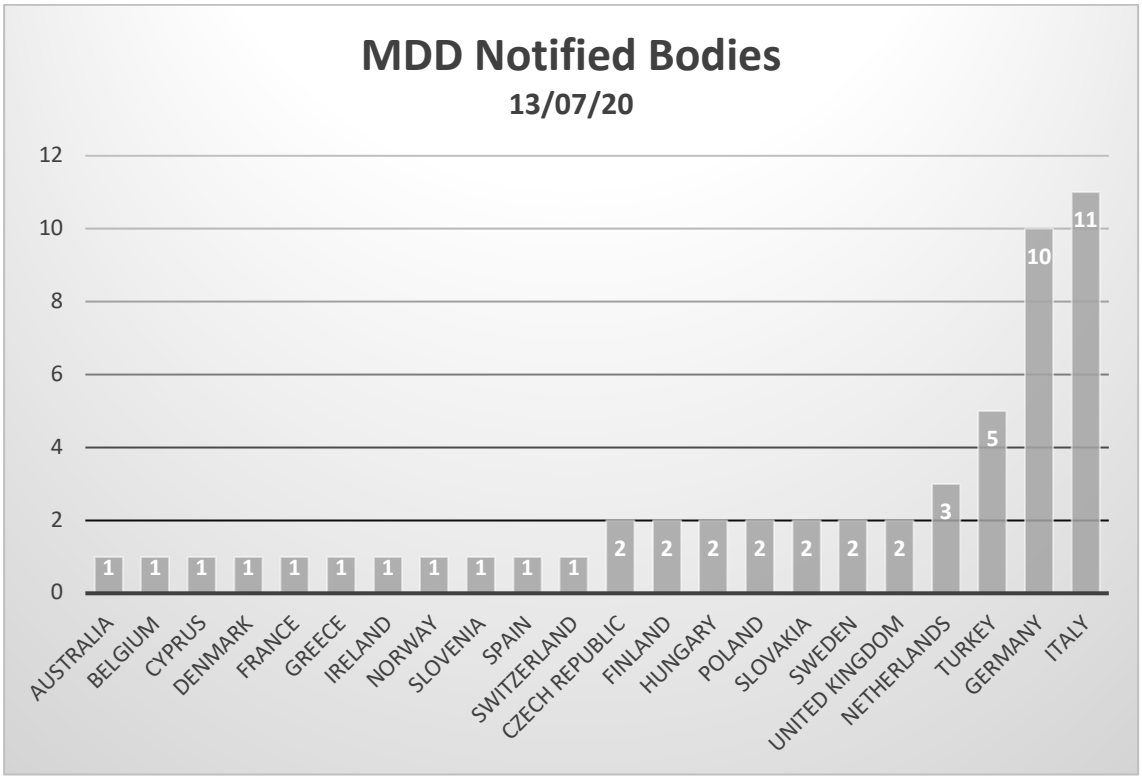

Figure 10.2. Bodies notified under the MDD, July 2020

The number of NBs in operation changes over time[i], as some are newly notified, others withdraw, or allow their notification to elapse, whilst others may be in the process of renewing theirs. In 2012, there were seventy-six NBs.[429] In August 2021, there were twenty-three notified bodies designated under the MDR[ii], and six under the IVDR[iii], with nine still notified under the AIMDD[iv], 50 under the MDD[v], and eighteen under the IVDMDD[vi]. In total there were fifty-five individual organisations notified under one or other of these directives or regulations (since some are notified under more than one legislation), with fifty-three in total under the directives and twenty-two in total under the regulations. By 13 July 2021, there were fifty-four notified under the MDD, whilst seventy

[i] In 2018 there were 59 NBs designated under the MDD, this reduced to 58 in 2019, 56 in early 2020, and down to 54 by July 2020. Eight NBs were not listed in July 2020 that were listed in 2018, the notification expired for two NBs, but the others all withdrew their applications to be notified bodies (under the MDD, although they could potentially still be notified under other directives).There were three NB that were listed in July 2020 that weren't listed in 2018.

[ii] https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=34

[iii] https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=35

[iv] https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=8

[v] https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=13

[vi] https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=20

had withdrawn notification or it had expired, 'withdrawn/expired', or had been suspended. As of 21 September 2023, there were ten NBs notified under the AIMDD, fifty for the MDD, nineteen for the IVDMDD, thirty-nine under the MDR, and eleven for the IVDR, with just fifty-seven NBs altogether. As can be seen, there is still a shortfall in the number of NBs available to perform conformity assessment procedures under the MDR and IVDR compared with the numbers that were previously available for these tasks under the MDDs.

Bodies are notified under particular directives or regulations (as listed on the NANDO webpage), to perform specific conformity assessment procedures for specific categories of medical device. They are also notified for specific competencies, called horizontal technical competences. These different areas are listed in Tables 10.3-10.5. The tables show that not all NBs are notified for all aspects of assessment, nor are they all notified for all product classes.[i]

Table 10.3. Specific procedures for which a body may be notified

Specific procedures for which a body may be notified under the MDD (Numbers notified as of 13 July 2020)		
Annex	***Conformity Assessment Procedure***	No. of NBs
Annex II	EC Declaration of conformity (full quality assurance)	54
Annex VI	EC Declaration of conformity (product quality assurance)	45
Annex V	EC Declaration of conformity (production quality assurance)	54
Annex III	EC type-examination	20
Annex IV	EC verification	20
Annex II	Full quality assurance system (22/11/2010)	54
Annex VI	Product quality assurance (22/11/2010)	45
Annex V	Production quality assurance (22/11/2010)	54

[i] For example only 38 NBs are notified under Directive 93/42/EEC to conduct a Product quality assurance of non-active orthopaedic devices; and only 34 are notified to conduct a Full quality assurance procedure (Annex II) for absorbable orthopaedic implants. Forty nine NBs are notified to conduct a full quality assurance of software devices, but only 18 are notified to conduct an EC type-examination (Annex III), and NSAI is not one of those 18 since it is not notified to perform EC type-examination, although it is notified for all the previous examples.

Table 10.4. Specific products for which a body may be notified

Specific product categories for which NBs may be notified under the MDD	
Product code	***Product type***
MD 0100	General non-active, non-implantable devices
MD 0101	Non-active devices for anaesthesia, emergency and intensive care
MD 0102	Non-active devices for injection, infusion, transfusion and dialysis
MD 0103	Non-active orthopaedic and rehabilitation devices
MD 0104	Non-active medical devices with measuring function
MD 0105	Non-active ophthalmic devices
MD 0106	Non-active instruments
MD 0107	Contraceptive medical devices
MD 0108	Non-active devices for disinfecting, cleaning, rinsing
MD 0109	Non-active devices for in vitro fertilisation (IVF) and assisted reproductive technologies (ART)
MD 0110	Non-active medical devices for ingestion
MD 0200	Non-active implants
MD 0201	Non-active cardiovascular implants
MD 0202	Non-active orthopaedic implants
MD 0203	Non-active functional implants
MD 0204	Non-active soft tissue implants
MD 0300	Devices for wound care
MD 0301	Bandages and wound dressings
MD 0302	Suture materials and clamps
MD 0303	Other medical devices for wound care
MD 0400	Non-active dental devices and accessories
MD 0401	Non-active dental equipment and instruments
MD 0402	Dental materials
MD 0403	Dental implants
MD 1100	General active medical devices
MD 1101	Devices for extra-corporal circulation, infusion and haemophoresis
MD 1102	Respiratory devices, devices including hyperbaric chambers for oxygen therapy, inhalation anaesthesia
MD 1103	Devices for stimulation or inhibition
MD 1104	Active surgical devices
MD 1105	Active ophthalmological devices
MD 1106	Active dental devices
MD 1107	Active devices for disinfection and sterilisation
MD 1108	Active rehabilitation devices and active prostheses
MD 1109	Active devices for patient positioning and transport
MD 1110	Active devices for in vitro fertilisation (IVF) and assisted reproductive technologies (ART)
MD 1111	Software
MD 1112	Medical gas supply systems and parts thereof
MD 1200	Devices for imaging
MD 1201	Imaging devices utilising ionizing radiation
MD 1202	Imaging devices utilising non-ionizing radiation
MD 1300	Monitoring devices
MD 1301	Monitoring devices of non-vital physiological parameters
MD 1302	Monitoring devices of vital physiological parameters
MD 1400	Devices for radiation therapy and thermo-therapy
MD 1401	Devices utilising ionizing radiation
MD 1402	Devices utilising non-ionizing radiation
MD 1403	Devices for hyperthermia/hypothermia
MD 1404	Devices for (extracorporeal) shock-wave therapy (lithotripsy)

Table 10.5. Specific competences for which a body may be notified

Specific competences for which an NB may be notified under the MDD (Numbers notified as of 13 July 2020)		
Code	***Horizontal technical competences***	Number
MDS 7001	Medical devices incorporating medicinal substances, according to Directive 2001/83/	35
MDS 7002	Medical devices utilising tissues of animal origin, including Regulation 722/2012 (Directive 2003/32/EC u…	23
MDS 7003	Medical devices incorporating derivatives of human blood, according to Directive 2000/70/EC amended by Directive ..	9
MDS 7004	Medical devices referencing the Directive 2006/42/EC on machinery	46
MDS 7006	Medical devices in sterile condition	51
MDS 7007	Medical devices utilising micromechanics	16
MDS 7008	Medical devices utilising nanomaterials	17
MDS 7009	Medical devices utilising biological active coatings and/or materials or being wholly or mainly absorbed	34
MDS 7010	Medical devices incorporating software/utilising software/controlled by software	52

Under the MDR, there were fifteen bodies notified on 13 July 2020; of these five were in Germany, three in the Netherlands, and one in each of France, Hungary, Ireland, Italy, Norway, Sweden and the United Kingdom. By July 2020, when the MDR was expected to have entered into full force, there were just fifteen bodies notified under the MDR compared with 59 notified previously under the MDD in 2018, leaving a large shortfall in the number of NBs available to perform the CAPs required under the MDR.

This meant that, in effect, NBs were no longer competing with each other due to the very high volume of work induced by the additional requirements imposed on economic operators and NBs as well as the hugely reduced number NBs available to do the work. The designation process is slow and some countries have fared less well than others with regard to how fast their NBs were able to become compliant with the requirements imposed on them by the MDR. Ireland's NB has been designated under both the MDD and the MDR, and it was the eleventh NB to be designated under the MDR.

Figure 10.3 compares the numbers of NBs designated under the MDD with the numbers designated under the MDR by July 2020. It reveals the significant shortfall in the number of NBs available to assess the conformity of medical devices under the MDR, with just 15 compared with 54 under the MDD. Furthermore, most countries had no NBs designated under the MDR, though 22 had NBs designated under the MDD. Additionally, based on the number of NBs designated under the MDD, it highlights that Italy, Germany, and Turkey were key locations for economic operators to have their devices assessed under the MDD, each having 11, 10, and 5 NBs respectively. Finally, it shows that Italy

and Turkey had only one NB designated under the MDR between them by July 2020, which significantly disadvantaged those manufacturers who normally have their conformity assessments conducted or verified by those NBs. The graph also shows that only Ireland, France, the Netherlands and Norway have as many NBs notified under the MDR as were notified under the MDD.

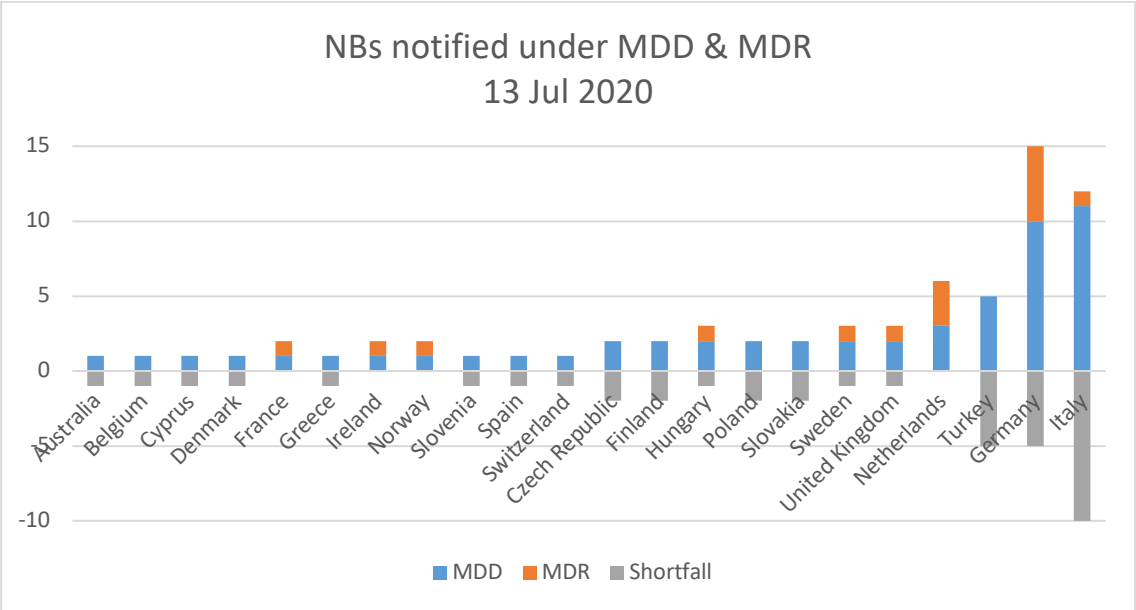

Figure 10.3. Notified Bodies designated under the MDD and MDR by 13 July 2020

As of April 2024, there are now 45 NBs notified under the MDR, which still presents a shortfall in the required numbers, which is likely to mean that NBs are still not competing with one another again yet. It also means that the NBs actually have more power to place demands on the manufacturers regarding requests for more tests or documentation, or meeting expected standards or requirements, since they do not have to be concerned about manufacturers going elsewhere.

10.1.4. Competent Authorities & National Competent Authorities (NCAs)

A Competent Authority (CA) is an authority designated by MS as responsible for carrying out market surveillance on its territory.[407, Article 2(18)] They are responsible for receiving and reviewing manufacturer and user incident reports, field safety notices (FSNs) and corrective actions (FSCAs) by manufacturers, monitoring safety signals, and communicating concerns regarding any unexpected new AMDEs or any change in the usual pattern of incidents (trend changes) to other CAs through National Competent Authority Reports (NCARs) Exchange Programs. CAs are also responsible for authorising clinical investigations for CE marking on medical devices in their territory.

For the most part, CAs have a national remit, but not always. As of September 2023[i], there were 67 CAs listed in EUDAMED, with Germany having 34, Croatia and the Netherlands each having two, and all other MS having one each, including one for Northern Ireland.

10.1.1. Umbrella organisations

In addition to European and national regulatory authorities, umbrella organisations exist both at national and international level. These aim to harmonise the application of regulatory rules and act as a form of soft regulation via a system of peer review, with many of them issuing guidance or supporting documentation for their members.

10.1.1.1. Notified Bodies Operations Group (NBOG)

The NBOG was set up in 2000 to address concerns regarding the variability in practice and competence of NBs and their DAs. Its remit was to improve the performance of NBs primarily by identifying and promoting best practices for NBs and DAs. Its membership is composed of the Commission, and nominees from the Notifying Authorities/Competent authorities of MS and EFTA/EEA, Candidate and Accession countries. It is chaired by a representative of the CAs (elected by CAs), meets twice a year in Belgium, and is hosted by the Commission. Its main work is to produce guidance (through a process of drafting, consultation, and consensus on a final draft amongst the group) but it also provides and facilitates training for use by NAs, promotes relevant IMDRF documentation for NBs, and is responsible for establishing a peer review system for NAs. NBOG has also taken an advocacy role for promoting and safeguarding medical device safety by submitting resolutions to the EU Commission concerning device safety.[ii]

10.1.1.2. Competent Authorities for Medical Devices (CAMD)

CAMD is composed of the NCAs of MS. It was established in 2012 following the PIP breast implant scandal[iii] to work as an umbrella body to improve market surveillance, collaborative working, and communication between the national competent authorities for medical devices as part of the PIP Action Plan.[430] This focussed on improving the functioning of NBs, increasing communication and transparency, and sharing good practices between NCAs.[431] CAMD sets up Joint Actions between its members to meet these objectives. The Joint Actions (and associated work by Working Groups) are

[i] 21st September 2023. However, this has changed since August 2021, when there were 61 CAs. with one per member state apart from Germany, which had 31, and also one each for Liechtenstein, Norway, and Northern Ireland. https://ec.europa.eu/tools/eudamed/#/screen/competent-authorities

[ii] [Internet]. Accessed 2021 Sep 25. Available from: https://www.nbog.eu/nbog-reports-and-news/

[iii] These implants had a higher than normal rate of rupture and it was discovered that the manufacturer was using industrial grade rather than medical grade silicon.

coordinated by the CAMD Executive Group (CEG)[i], which has nine members - seven elected, and two representing the current and incoming host countries for the European Presidency.[430]

10.1.1.3. Team-NB

Team NB is the European Association of Notified Bodies for medical devices. Membership is voluntary and is open to subscribing NBs. In 2023, it has 37 members (29 in 2021, 25 in 2020) notified under any of the medical device directives or regulations[ii]. It was established in 2001 and produced its first code of conduct for NBs in 2012.[432] All members must sign up to the current code of conduct (Personal communication[iii]). Team NB creates guidance documents for its members on methods related to the process of assessing the conformity of medical devices with the relevant directives and/or regulations.[iv]

10.1.1.4. European Co-operation for Accreditation - European Accreditation (EA)

The EA is the European association of national accreditation bodies (NABs) designated by their MS to assess organisations that carry out conformity assessment or evaluation services (such as certification, verification, inspection, testing and calibration), and verify their compliance with the relevant international standards in the ISO/IEC 17000 series.
The EA provides a means of peer evaluation of its members, and to become a member requires an evaluation of the applicant NAB's competency, the agreement of members to recognise accreditations conducted by the applicant NAB (a multi-lateral agreement referred to as MLA), and the signing of that agreement by the applicant NAB.[433]

10.1.1.5. Standards Organisations

There are a number of standards authorities. The European Standards Organizations (ESO) is a group of three standards organisations – the European Committee for Standardization (CEN), the European Committee for Electrotechnical Standardization (CENELEC) and the European Telecommunications Standards Institute (ETSI). They bring together the relevant standards bodies of the EU MS and other partners, such as signatories of the European Free Trade Association (EFTA), to discuss and agree on standards. European Standards, called European Norms (ENs), are those that have

[i] [Internet]. Accessed 2021 Sep 24. Available from: https://www.camd-europe.eu/camd-aims-and-objectives/
[ii] [Internet]. Accessed 2023 Sep 22. Available from: https://www.team-nb.org/members/
Also Accessed 2021 Sep 24. Available from: https://www.team-nb.org/wp-content/uploads/2020/09/TEAM-NB-Member-List-28.pdf
[iii] Information received from an NB representative at the 2nd Workshop of the EUnetHTA Task Force on HTA and Medical Devices, 28 May 2019, in Vienna.
[iv] This website lists their guidance documents at: https://www.team-nb.org/team-nb-documents/

been ratified by one of the three ESOs and once ratified supersede any equivalent national standards. A harmonised standard (HS) is a European Standard that has been '*adopted on the basis of a request made by the Commission for the application of Union harmonisation legislation'*, so that it can be used to demonstrate that a product (or service or process) is compliant with the relevant EU legislation, and when HS are used, conformity with the relevant ER(s) must be presumed.[434, Article 2, 1(c)]

The ESOs don't sell the harmonised (or other) standards. Once a European standard or EN, is published, the national standards organisations of the EU member states, Switzerland and Turkey are legally required to implement and publish it as a national standard, and it is they who sell them.

The ESOs also cooperate with the International Standards Organization (ISO) to produce internationally applicable standards. When a standard is harmonised between the EU and the ISO this is indicated in the name, which includes EN and ISO. For example, when CEN adopted ISO 14971:2019, the ISO risk management standard for medical devices, it became EN ISO 14971:2019. Similarly, when national standards bodies adopt the EN standards to provide them for sale at national level they also add their national identifier. For example, when adopted as the Irish Standard by the NSAI EN ISO 14971:2019 became I.S. EN ISO 14971:2019 and when adopted by the British Standards Institute (BSI) it became BSI EN ISO 14971:2019. Standards are subject to copyright and are not freely available. They must be bought, making it difficult to share their contents; however the table of contents for each standard is publicly available on the ISO website. The fee for I.S. EN ISO 14971:2019 is €69.00 for members, whilst it costs £127.00 (£254.00) for non-members to obtain the BSI EN ISO 14971:2019.[435,436]

The ESOs provide references to standards but they don't sell them, instead they each provide links to national standards organisations who provide the standard for sale.

10.1.2. Additional actors involved in implementing the MDR

In addition to the above organisations, the MDR introduces several new actor groups – the Medical Device Coordination Group (MDCG), Expert Panels, Expert Laboratories, and the Person responsible for regulatory compliance (PRRC), whose involvement should improve the quality, and potentially the clinical effectiveness, of devices.

10.1.2.1. Medical Device Coordination Group (MDCG)

The MDCG is an expert committee set up to help the Commission to ensure '*a harmonised implementation of this Regulation*', by providing the expertise[i] needed.

[i] Alternatively, they may set up sub-groups '*in order to have access to necessary in-depth technical expertise'*

The MDCG is composed of an expert and an alternate from each MS with expertise in medical devices and one expert and an alternate with expertise in *in-vitro* diagnostic devices[i], who are appointed for a three year, renewable, term.[3, Article 103, 2] Similar to other committees, the MDCG is responsible for establishing its rules of procedure. The MDCG represents the NCAs. They meet at regular intervals and may form working sub-groups to carry out their tasks, which are set out in Article 105.[3, Article 105] These are to contribute to: the assessment of NBs and CABs applying for notification; the development of guidance for implementing the MDR[ii], the development of standards, CS, and scientific guidelines on clinical investigations of particular implantable devices and class III devices; the harmonisation of administrative practices for medical devices amongst MS; and the continuing monitoring of technical progress to maintain the adequacy of the GSPRs to ensure the 'safety and performance' (not effectiveness, it appears that they have not been given that remit!) of medical devices They must also assist the CAs in developing and maintaining a market surveillance programme for Europe and in coordinating their activities[iii]. Finally, they are to advise the Commission regarding the coordination group of NBs (CGNB-Med) and provide advice on implementation issues related to the MDR.

There are currently thirteen working groups (WG) as shown in Box 10.1.

MDCG Working Groups:

1. Notified bodies oversight (NBO)
2. Standards
3. Clinical investigation and evaluation (CIE)
4. Post-market surveillance and vigilance (PMSV)
5. Market Surveillance (MS)
6. Borderline and classification (B&C)
7. New technologies
8. EUDAMED
9. Unique device identification (UDI)
10. International matters
11. In vitro diagnostic medical devices (IVD)
12. Nomenclature
13. "Annex XVI" products

Box 10.1. List of MDCG Working Groups (February 2024)

[i] MS may choose to send a single expert and alternate with expertise in both.

[ii] Particularly regarding the designation and monitoring of NBs, application of the GSPRs, conduct of clinical evaluation and clinical investigations by manufacturers, assessment by NBs, and vigilance activities.

[iii] Activities related to classification, determining the regulatory status of products, clinical investigations, vigilance, and market surveillance.

The WGs may invite organisational representatives to participate in the sub-groups as observers. The MDCG members do not have to reach consensus to determine the position of the group, but they should seek to do so. When this is not the case the MS may request that the diverging positions, and their reasons for divergence, be recorded in the MDCG's position. To date[i] they have produced 139 guidance documents[ii] (including some revisions), enumerated according to WGs in Table 10.6.

Table 10.6. MDCG Guidance produced to date (12th April 2024)

MDCG-WG	Number
Custom-made Devices	1
In-house Devices	1
Person responsible for regulatory compliance (PRRC)	1
Standards	1
Class I Devices	2
Implant Cards	2
Annex XIV products	3
Economic Operators	3
Borderline & Classification	5
New Technologies	5
EUDAMED	6
European Medical Device Nomenclature (EMDN)	6
Other	7
Post-Market Surveillance and Vigilance (PMSV)	8
COVID-19	11
Unique Device Identifier (UDI)	13
In Vitro Diagnostic medical devices (IVDs)	16
Clinical Investigation & Evaluation	17
Notified Bodies	31
Total	**139**

10.1.2.1. Expert Panels and Expert Laboratories

Article 106 of the MDR empowers the Commission to establish expert panels and expert laboratories, temporarily or permanently, choosing experts with the relevant expertise, drawn from the respondents to a call for expressions of interest or from a panel created from respondents to such a call. Expert panels must be constituted to reflect the EU's

[i] April 12th 2024

[ii] The guidance documents are available at: https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en#sec10

geographical variation and its diversity of 'scientific and clinical approaches'. Conflicts of interest are to be actively managed (and prevented) by the Commission.

The expert panels and expert laboratories are to provide assistance in implementing the MDR. Specifically, they are to contribute to: the identification of any concerns and emerging issues; the development of standards (at an international level), CS, and guidance (related to clinical evaluation, PMCF, investigations, pre-clinical testing, performance evaluation, and post-market performance follow-up); and develop and review clinical evaluation guidance and performance evaluation guidance for conformity assessment.

10.1.2.2. Person responsible for regulatory compliance

The PRRC is unique to the EU. The MDR introduced a requirement, in Article 15, that manufacturers and ARs have available within their organisation[i] a person designated as the PRRC. The PRRC must be sufficiently qualified for the task[ii].

The PRRC is responsible for ensuring that the conformity of devices is checked against the QMS before being released; the technical documentation and EU declaration of conformity are drawn up and kept up-to-date, the statement required for investigational devices (stating that apart from those aspects being investigated, the GSPRs have been met, and for those aspects being investigated every precaution has been taken to protect the health and safety of the subject); and the obligations related to the PMS and vigilance (Articles 10(10) and 87-91) are fulfilled. These responsibilities may be subdivided amongst a number of designated PRRC, but if so, then their respective responsibilities must be specified In writing.

The MDR also mentions two other new groups of actors, but says very little about either, these are the NB coordinating group[iii], and the entities designated to issue UDIs.

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[i] In the case of SMEs, the PRRC need not be within the organisation, but must be 'permanently and continuously at their disposal'.

[ii] The PRRC must have a university degree or equivalent qualification from a recognised course of study in law or a relevant scientific discipline and at least one years' experience in regulatory affairs or in quality management systems related to medical devices, alternatively, they need not have a qualification if they have at least four years' experience. For manufacturers of custom-made devices the PRRC need only have two years' experience, but this must be in a relevant field of manufacturing.

[iii] The Commission provides a little information on its website, explaining that the NB coordinating group established by Article 49 of the MDR is called NBCG-Med and that it has a technical sub-group (with two sections, one each for the MDR and the IVDR). Apart from providing a forum for sharing experience and views between NBs, creating consistency, and providing advice to the Commission and MDCG, NBCG-Med drafts technical recommendations and creates consensus relating to conformity assessment and NB's activities. https://health.ec.europa.eu/medical-devices-dialogue-between-interested-parties/overview_en Team-NB have a page on their website listing NBCG-Med documents, but these go back as far as 2008, with the titles attributing them to NB-Med, which would suggest that NBCG-Med is the legal formalisation of NB-Med, but as Team-NB disclaims any responsibility for the documents that would suggest they are not the same entity: https://www.team-nb.org/nb-med-documents/

10.2. Implementation Process

The first step in the implementation process for the MDD involved transposing EU regulation into national law, however, the MDR is immediately effective in national law. The next step is providing guidance on implementation (to manufacturers and regulatory authorities) and enforcement (to regulatory authorities), implementing standardised processes (e.g. quality management systems and risk management), and assessing compliance.

Some of the key processes involved in implementing the MDDs (and the MDRs), as specified in the legal framework, include the development and use of harmonised standards,(Article 3; Annex I & Article 5) CE marking,(Article 17; Annex XII) device classification,(Article 9; Annex IX) conformity assessment,(Article 11; Annexes II-VII) declaration of conformity,(Article 11; Annexes II, V-VII) provision of clinical data (clinical evaluation and clinical investigations),(Article 15; Annex X) and post market surveillance and vigilance.(Article 10; Annexes II, IV-VII, X)

10.2.1. Transposition into national legislation

The transposition of EU directives into national legislation varies across countries, in terms of its timing and wording. Ireland transposes EU Directives into law through the publication of Statutory Instruments (S.I.). The MDD was transposed into national law in Ireland, as S.I. 252 of 1994, whilst the AIMDD and the IVDMDD were transposed as S.I. 253 of 1994 and S.I. 304 of 2001, respectively. Since the AIMDD was enacted in 1990, the MDD in 1993, and the IVDMDD in 1998, this highlights the delay that can occur between the enactment of an EU directive and its transposition into MS national law. Indeed, it appears Belgium only transposed the MDD in 1999.[437]

10.2.2. Medical device guidelines and guidance

The Medical device guidelines or MEDDEVs are a set guidelines developed by the European Commission (EC) to assist with compliance of the medical device directives. They are not legally binding but as they have been developed through a consultative process with industry, regulators and other interested parties, they are considered to reflect their positions and the current ‘state of the art’. Whilst they are not legally binding, and it may be possible to meet the essential requirements in other ways, it is expected that, for the most part, these guidelines will be followed. The MEDDEVs are freely available on the Commission website.[i]

The MEDDEVs also undergo revision, and when this is the case these revisions are numbered and included in the document reference. For example, MEDDEV 2.1/3 rev.3

[i] https://health.ec.europa.eu/system/files/2022-01/md_guidance_meddevs_0.pdf

is the updated guideline on *Borderline products, drug-delivery products and medical devices incorporating, as integral part, an ancillary medicinal substance or an ancillary human blood derivative*.[438] There are 30 MEDDEVs available to support manufacturers in complying with the legal requirements. The MEDDEV series are listed in Table 10.7.

Table 10.7. MEDDEV series of guidelines

Series	Topic area
2.1	Scope, field of application, definition
2.2	Essential requirements
2.4	Classification of Medical Devices
2.5	Conformity assessment procedure
2.7	Clinical investigation, clinical evaluation
2.10	Notified bodies
2.12	Post-Market surveillance
2.13	Transitional period
2.14	IVD
2.15	Other guidance

Other EC resources provided to guide compliance or conformity assessment include reporting templates (e.g. trend reporting of safety issues, periodic safety updates, etc.), manufacturing incident report forms (MIR), or interpretative documents.

The MDR established the Medical Devices Coordination Group (MDCG) shifting the remit to develop guidance to this group. The MDCG has done a lot of work done since then, preparing guidance documents to support the implementation of the MDRs. Their guidance is referred to as MDCG endorsed documents or guidance rather than MEDDEVs, some of which they replace or update. The MDCG had produced 139 guidance documents by April 12th 2024.

10.2.3. Standards

A standard is a '*document, established by consensus and approved by a recognized body, that provides, for common and repeated use, rules, guidelines or characteristics for activities or their results, aimed at the achievement of the optimum degree of order in a given context'.*[439] Standards are important for ensuring high quality, clear communication on specifications, and compatibility of products with other products that they need to interact with, or where one is dependent on another for its proper functioning. A simple example of this is a device that requires electricity in order to function. It simply won't work if the plug doesn't fit the socket, nor will it work (at least not safely) if the voltage is incompatible. So the dimensions of the plug and the socket are standardised to ensure that they are compatible, fitting and working safely together.

Standards are created by different organisations, and they may be created for various levels of application (e.g. standards set within an individual organisation, such as standard operating procedures versus those set across an industry (i.e. industry standards), or at a national, European, or international level by the national, European, or international standardisation bodies. Furthermore, standards may apply to a broad range of products (horizontal standards) or to specific products (vertical standards).

There are over 22,000 internationally accepted standards published in the ISO catalogue.

Publication of references to the standards in the OJ is required to give them legal status as harmonised standards (HS), providing presumption of conformity with the ERs (or parts thereof) that they address. Since 1 December 2018 the list of HS has been published in the OJEU by means of Commission Implementing Decisions. In 2020, the list for the MDD was updated in Commission Implementing Decision (EU) 2020/437 of 24 March 2020 and remains valid until 26 May 2024.[390] Box 10.2 lists some of the key standards for medical devices. Two key horizontal standards that all manufacturers of medical devices should implement are ISO 13485 on the Quality management system (QMS) required for medical devices (specifically the requirements of the QMS for regulatory purposes), and ISO 14971 on the application of a risk management process to medical devices, which was described in Chapter 7 (section 7.1.2.3).

HS are developed by technical committees (TCs) '*through a process of sharing knowledge and building consensus among technical experts nominated by interested parties and other stakeholders - including businesses, consumers and environmental groups, among others*.'[439] Thus, membership includes industry actors, and though it is difficult to find out to what extent they influence standards development, NSAI's Healthcare Standards Committee, TC5, which provides a national forum for stakeholders to review the standard developments for healthcare and medical devices and monitors the work of TCs involved in developing medical device-related standards, lists forty-three members, at least twenty-seven of whom represent industry.[440 p.6]

Table 10.8 lists some of the most relevant TCs involved in developing standards relevant to medical devices, followed by a brief summary of the most relevant standards required for most medical devices.

Table 10.8. CEN Technical Committees: Technical bodies and activities

CEN Technical Committees: Technical bodies and activities	
CEN/CLC/JTC 16	Joint Technical Committee on Active Implantable Medical Devices
CEN/CLC/JTC 3	Quality management and corresponding general aspects for medical devices
CEN/SS S02	Transfusion equipment
CEN/SS S03	Syringes
CEN/SS S99	Health, environment and medical equipment - Undetermined
CEN/TC 102	Sterilizers and associated equipment for processing of medical devices
CEN/TC 140	In vitro diagnostic medical devices
CEN/TC 170	Ophthalmic optics
CEN/TC 204	Sterilization of medical devices
CEN/TC 205	Non-active medical devices
CEN/TC 206	Biological and clinical evaluation of medical devices
CEN/TC 215	Respiratory and anaesthetic equipment
CEN/TC 216	Chemical disinfectants and antiseptics
CEN/TC 239	Rescue systems
CEN/TC 285	Non-active surgical implants
CEN/TC 293	Assistive products for persons with disability
CEN/TC 392	Cosmetics
CEN/TC 55	Dentistry
CLC/TC 62	Electrical equipment in medical practice
[Internet]. Accessed 2020 Sept 20. Available from: https://www.cen.eu/work/Sectors/Healthcare/Pages/Medicalequipment.aspx[441]	

10.2.4. CE Marking

In order to place a medical device on the EU market, the manufacturer or its authorised representative (AR) must first obtain a CE marking for the device. NSAI[i] outlines ten steps for manufacturers to follow to acquire the CE marking, summarised below:

1. Identify the applicable directives for the device;
2. Identify the conformity assessment procedure that must be taken;
3. Determine which requirements must be met, and when[ii];
4. Identify any Harmonized Standards[iii] applicable to the device;
5. Ensure the device complies with all the essential requirements of the applicable legislation. Take appropriate measures to comply or identify existing data and test reports;
6. Identify if a notified body must be involved in the conformity assessment procedure;
7. Maintain the device's technical documentation required by the Directive(s)/Regulation(s)[iv];

[i] https://www.nsai.ie/certification/nsai-certification/ce-marking/
[ii] Some legislative requirements are in transition, which allows the manufacturer choice between the older and newer requirements
[iii] These are not mandatory, but recommended as they confer a presumption of conformity with the particular essential requirement that they cover;
[iv] Necessary evidence for supporting claims of compliance with ERs/GSPRs.

8. Prepare the Declaration of Conformity and the required technical documentation, which must be kept available for inspection by the Competent Authorities (EU Members) if requested;
9. Check for any additional national requirements of MS where the device is to be sold, such as national standards for labelling or packaging (MS are entitled to require these to be made available in their own language or in another MS language for their users);
10. Affix CE Marking to the device and/or its packaging and accompanying literature.

From an industry perspective, the first step is to determine if the product is a medical device (i.e. does it meet the legal definition contained in the MDD/MDR)[i]. The MDR contains a broader definition than the definition contained in the MDD. The next step is to classify the device according to its level of risk by applying the classification rules (Annex IX of the MDD, Annex VIII of the MDR). Then the manufacturer must identify the CAPs allowable for that class of device, and choose which to use.

10.2.5. Conformity assessment

There are several conformity assessment procedures that the manufacturer may choose from to demonstrate conformity with the ER or the GSPR, but which of these is available for a given medical device is dependent on the device's classification. These are summarised in Table 10.10, whilst Table 10.11 shows the certificates that an NB may issue according to the relevant CAP.

Conformity assessment under the MDD

Annex VII is the simplest and least onerous CAP in the MDD. It is simply the EC Declaration of Conformity (DoC) that a manufacturer must make to attest to the conformity of the device with the relevant ERs. This procedure may be used on its own for declaring the conformity of Class I devices that do not have a measuring function and are not intended to be sterile. It requires the preparation of the technical documentation and a systematic procedure for PMS *'to review experience gained from devices in the post-production phase'*, including the reporting of serious incidents to the NCA. The extent and depth of this systematic procedure is not defined by the MDD. The technical documentation should include: a description of the device(s); intended uses; design drawings; manufacturing methods; results of the risk analysis; a description or list of the means (such as standards) used to achieve the ERs; the means used to ensure that the design and manufacture *'conform to the safety principles, taking account of the generally*

[i] Although the focus of most of this research has been on the MDD, nevertheless, although certificates issued under the MDD are still valid, any applications submitted for CE making must comply now with the MDD rather than the MDR.

acknowledged state of the art'; the pre-clinical evaluation; the clinical evaluation; the label; and the instructions for use.

Annex III provides a mechanism for manufacturers to have a prototype of their device examined by an NB to ascertain and certify that a representative sample fulfils the legal requirements. The NB issues a 'Type-Examination' certificate, and to complete the CAP manufacturers must also apply the procedure described in one of the three Annexes assessing the 'production phase', Annexes IV-VI. However, only Annexes IV or V may be used for Class III devices.

Annex II is the 'strictest' CAP in the MDD, requiring a QMS for all phases of a device's lifecycle (design, manufacture, and the final inspection and product testing processes). Similarly, Annex V, the EC Declaration of Conformity (Production quality assurance), and Annex VI, the EC Declaration of Conformity (Product quality assurance), require the manufacturer to establish a QMS, but Annex V need only apply this to the manufacturing and the final inspection and product testing processes, whilst Annex VI only requires that it is applied to the latter. Each of these Annexes requires verification, audit, and surveillance of the QMS by an NB. Manufacturers must apply to an NB of their choice for assessment of their QMS. They must also maintain technical documentation in a technical file for each device/device category (and kept available for inspection by the NCA), which must be included in their application. The application must include an undertaking by the manufacturer to comply with the obligations of the QMS, maintain and update the QMS to ensure its effectiveness, institute a systematic process for PMS and corrective actions; and that they will report any serious AMDEs associated with either device to the relevant NCAs. Additionally, they must also submit their DoC, which for Annex II includes a declaration that their device meets the relevant ER (and other legal requirements), whilst for Annex V and VI CAPs they declare that the device in question conforms to the type described in the relevant type-examination certificate. Any planned changes in the QMS (or the range of products covered) must be notified to the NB, who will assess if the QMS will still comply with the ER and if the certificate remains valid.

To meet the ERs (and the GSPRs), manufacturers must institute a risk management process, estimate the benefit-risk ratio for their device given its anticipated benefits for its intended purpose, determine the acceptability of any residual risks after risk elimination/reduction/mitigation, and conduct a clinical evaluation to provide 'clinical data' supporting their conclusions on the benefit-risk ratio and risk acceptability. The MDD does not require that the manufacturer establishes the efficacy of the device, only that it performs as intended.

The NB must audit the QMS and inspect the manufacturer's premises (and if justified, those of their suppliers). They must presume conformity with any ERs for which HS have been used. Following inspection they provide their decision on the inspection (containing a reasoned assessment and their conclusions) to the manufacturer. They may request additional tests be performed to prove compliance. Thereafter, the NB must perform surveillance of the QMS to check that the manufacturer is meeting the obligations imposed by their own QMS, including the conduct of periodic inspections and assessments. Following a successful CAP, the NB issues the appropriate certificate (see Table 10.10) and the manufacturer affixes the CE marking to their device, which allows them to market it in any EU country.

Table 10.9. Applicable conformity assessment procedures

	Relevant Annex (Procedure)					
Risk Class	**MDD**	**MDD alternative**		**MDR**	**MDR alternative**	
Class I	-	VII (EC Declaration of conformity)		-	EU declaration of conformity (Article 19) after drawing up the technical documentation set out in Annexes II and III	
Class I_s	-	VII (EC Declaration of conformity)	IV or V or VI (EC verification or Production QA or Product QA)	-	Chapters I and III of Annex IX, or in Part A of Annex XI	
Class I_m	-	VII (EC Declaration of conformity)	IV or V or VI (EC verification or Production QA or Product QA)	-	Chapters I and III of Annex IX, or in Part A of Annex XI	
Class IIa	II-(4) (Full QA apart from design module)	III (Type-examination)	IV or V or VI (EC verification or Production QA or Product QA)	Chapters I and III of Annex IX & Section 4[#]	Draw up the technical documentation set out in Annexes II and III[#]	Section 10 or Section 18 of Annex XI
Class IIb	II-(4) (Full QA apart from design module)	III (Type-examination)	IV or V or VI (EC verification or Production QA or Product QA)	Chapters I and III of Annex IX & Section 4[i*]	X	Product conformity verification, XI (Part B)
Class III	II (Full QA)	III (Type-examination)	IV or V (EC verification or Production QA)	IX (QMS & Technical Documentation ≈ Full QA)	X (Type-Examination)	XI (Product Conformity Verification : Part A ≈ Production QA; Part B ≈ Product QA)
Custom-made		VIII (Statement)		-	Annex XIII (Statement)	

[i] Assessing the technical documentation for at least one representative device per generic device group, but for all devices in the case of implantable devices (sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips and connectors)..

Table 10.10. Certificates issuable by NBs under the MDD and MDR according to the applicable conformity assessment procedure

Annex	Conformity Assessment Procedure	Certificate
Medical Device Directive		
II	EC Declaration of Conformity	EC Design-Examination Certificate
II, excluding section 4	EC Declaration of Conformity	EC Certificate of conformity (Full Quality Assurance)
III	EC Type-Examination	EC Type-Examination Certificate
IV	EC Verification	Certificate of conformity
V	EC Declaration of Conformity (Production Quality Assurance)	EC Certificate of conformity (Production Quality Assurance)
VI	EC Declaration of Conformity (Product Quality Assurance)	EC Certificate of conformity (Product Quality Assurance)
Medical Device Regulation		
IX, Chapter I	Conformity Assessment based on a Quality Management System and on Assessment Of Technical Documentation, Chapter I: Quality Management System Assessment	EU Quality Management System Certificate
IX, Chapter II	Conformity Assessment based on a Quality Management System and on Assessment Of Technical Documentation, Chapter II: Assessment Of The Technical Documentation	EU Technical Documentation Assessment Certificate
X	Conformity Assessment based on Type-Examination	EU Type-Examination Certificate
XI, Part A	Conformity Assessment based on Product Conformity Verification, Part A Production Quality Assurance	EU Quality Assurance Certificate
XI, Part B	Conformity Assessment based on Product Conformity Verification, Part B Product Verification	EU Product Verification Certificate

Whilst the Annex II procedure is preferable, it is also possible for manufacturers of Class IIb devices to use a type-examination certificate (Annex III) and apply Annex IV, the ‘EC

Verification' procedure. This again requires the manufacturer to provide a declaration that the products assessed conform to the design specifications set out in the type-examination certificate, but the NB is not required to assess their QMS, instead it tests the end-product, either all products or a sample of them to verify that they meet the design and manufacturing specifications described in the relevant type-examination certificate. The manufacturer must also undertake to institute a PMS system and notify their NCA of any serious AMDEs.

Conformity assessment procedures under the MDR

The MDR does not introduce a new system of pre-market approval of medical devices, not even for high-risk devices as had been called for. Instead it takes the same approach as that taken in the MDD, where manufacturers must meet the essential requirements, the GSPRs, institute a QMS, RMS, and PMS, make a declaration of conformity, and apply to an NB for assessment of their conformity with the legal requirements, be assessed for their conformity, before affixing the CE marking allowing them to market their device(s). The most stringent of the CAPs provided in the MDR is the procedure in Annex IX, which is summarised in Box 10.3, and summarised below. As will be seen, it does not differ greatly from Annex II except in the level of detail that must be provided by manufacturers to their NB when applying for assessment of their QMS and technical documentation.

Annex IX

The CAP described in Annex IX requires manufacturers to:

1. Establish QMS
2. Apply to NB for assessment of their QMS
3. Inform their NB of any planned changes to the QMS or its scope

The application is to include the QMS documentation, which includes much more detail on all the aspects previously required by Annex II of the MDD related to the identification of the device, the design and manufacturing processes, their verification tests, and the procedures for clinical evaluation, PMS, and adds a requirement for manufacturers to prepare a post-market clinical follow-up (PMCF) plan (or justify why one isn't needed). It also requires a draft of their DoC.

Apart from simply adding more details, Annex IX demands a description of the procedures to meet the obligations imposed by the QMS (and an undertaking to apply those procedures) and a detailed description of their PMS and their PMCF plan, as well as their procedures to keep these up-to-date. This contrasts with Annex II of the MDD, where manufacturers need only provide an undertaking to meet their obligations from their QMS and institute a PMS as part of their application to their MB for assessment of

their QMS. Another difference with Annex II of the MDD, is that Annex IX specifically requires manufacturers to include documentation on their clinical evaluation plan, and their procedures to keep this up-to-date.

Chapter I – QMS

(1) QMS to be established

(2) QMS assessment

1. Application for assessment of QMS
2. Implementation of QMS to ensure compliance with MDR
3. Audit (by NB)
4. Inform NB of any changes to QMS or devices covered.

(3) Surveillance (to ensure manufacturer meets the obligations of their QMS)

Chapter II – Assessment of technical documentation

(4) Assessment of technical documentation

(5) Specific additional procedures

1. Assessment procedure for certain class III & class IIb devices
2. Procedure for devices incorporating a medicinal substance
3. Procedure for devices utilising or incorporating tissues or cells of human origin or their derivatives
4. Procedure for devices utilising or incorporating tissues or cells or animal origin or their derivatives
5. Procedure for devices composed of bioabsorbable or locally dispersed substances

(6) Batch verification for devices incorporating medicinal substances derived from human blood or plasma

Chapter III – Administrative provisions

(7) Economic operators are to keep documents at the disposal of the NCA for 10 years after the last one has been placed on the market (or 15 in the case of implantables)

(8) MS assumes the responsibility set out in point (7), if the Economic operator goes bankrupt/ceases business

Box 10.2. Summary of the contents and requirements imposed by Annex IX

In addition to the assessment of the QMS, manufacturers must also apply to their NB for an assessment of their technical documentation. This requires the NB to:

- review the documentation on the design, manufacture, and performance (i.e. functionality) of the device
- carry out any necessary tests (or request them to be done) to allow them to assess conformity with the requirements of the MDR
- review the clinical evidence in the clinical evaluation and the clinical evaluation report (CER) (for which they may request external expert clinical input)
- assess the suitability of devices claimed to be equivalent for providing indirect evidence on the device being assessed

- assess the evidence to support any claims made by the manufacturer regarding the innovativeness of their device
- assess and verify the adequacy of clinical evidence to support manufacturers claims regarding the safety and performance requirements for the device, their determination of the benefit-risk ratio, their RMS, the IFU, user training, their PMS plan and their plans for PMCF (or their justification for not planning PMCF) and its adequacy
- determine if milestones need to be defined for updating, and the NB reviewing, the clinical evaluation based on PMS and PMCF data
- document their assessment in a clinical evaluation assessment report (CEAR)
- provide the manufacturer with a report on the technical documentation assessment, the CEAR, and an EU technical documentation assessment certificate (assuming the device conforms)

Again, if manufacturers plan to make any changes they must inform the NB, who will assess if the QMS and technical documentation still comply or if the changes could affect the safety and/or performance of the device or its prescribed conditions of use, requiring a supplement to the original certificate or a new CAP.

The tasks imposed on NBs conducting a CAP according to Annex IX include that they:

1. Audit the manufacturer's QMS (review QMS documentation, presume conformity where HS have been used but also check that these have been applied)
2. Inspect their premises (and those of their suppliers, if justified)
3. Assess technical documentation for devices
4. Conduct QMS surveillance (with some requirements differing according to the Class of device)

For all devices, the NB performs surveillance of the QMs to ensure manufacturers meet the obligations it imposes on them; conducts annual on-site audits of the premises; and where considered necessary, carry out tests) or ask to have them carried out) to check their QMS is working correctly; and carry out unannounced visits every five years to check the QMS and the conformity of the products. It may also conduct tests on devices obtained on the market.

Interestingly, and presumably because of the fraudulent use of industry-grade silicon by Poly Implant Prothèse that had been concealed from the assessing NB, TÜV Rheinland, NBs are now required to check that the quantities of essential components of the devices purchased by the manufacturer correspond with the numbers of devices actually produced. (Annex IX, (3.5))

However, despite the first GSPR specifying that devices are required to be safe and effective, Annex IX does not enforce this, nor do the other Annexes.

Annexes X-XI

Similarly, Annex X follows the same pattern as Annex III of the MDD, Annex XI Part A follows the same pattern as Annex V of the MDD, and Annex XI Part B follows the same pattern as Annex IV of the MDD. However, where manufacturers were required to institute a PMS, they are now also obliged to include a PMCF plan and documented procedures for ensuring compliance with vigilance and PMS obligations. Additionally, similar to Annex IX (3.5), Annex XI Part A requires that the component quantities used in Class III devices be verified.[3] [3] Annex XI Part A(7) 2nd para

10.2.6. Clinical evidence required for CE marking under the MDD

In order to demonstrate conformity with the ERs and to be approved for affixing the CE conformity marking to a device, manufacturers had to conduct a clinical evaluation. To understand the clinical evidence that is required for this there are three important concepts that need to be defined:

- Clinical data
- Clinical evaluation
- Clinical investigation

10.2.6.1. Clinical data

The MDD did not originally define these, though it refers to them, particularly in Article 15 and Annex X. However, following amendment the following definition was included:

‘‘*clinical data’ means the safety and/or performance information that is generated from the use of a device. Clinical data are sourced from:*

— clinical investigation(s) of the device concerned; or

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

— published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated;’(MDD as amended, Article 1, 2(k))

Annex I was also amended, adding as an essential requirement that a clinical evaluation be conducted according to Annex X (6), necessary for demonstrating conformity. Apart from the above, Annex X provides very little information regarding what is considered to be clinical data or how to generate, gather, and synthesis it. This is left to the MEDDEVs and GHTF/IMDRF guidelines, the most relevant of which are listed in Table 10.11.

Therefore, I drew on these to understand the evidence that manufacturers are expected to submit in an application to the NBs for assessment of their conformity.

10.2.6.2. Clinical evaluation

Annex X did not provide a definition for clinical evaluation, but under its heading, 'CLINICAL EVALUATION 1. General provisions', it states that:

'1.1. As a general rule, confirmation of conformity with the requirements concerning the characteristics and performances referred to in Sections 1 and 3 of Annex I under the normal conditions of use of the device and the evaluation of the undesirable side-effects must be based on clinical data in particular in the case of implantable devices and devices in Class III. Taking account of any relevant harmonized standards, where appropriate, the adequacy of the clinical data must be based on:

1.1.1. either a compilation of the relevant scientific literature currently available on the intended purpose of the device and the techniques employed as well as, if appropriate, a written report containing a critical evaluation of this compilation;

1.1.2. or the results of all the clinical investigations made, including those carried out in conformity with Section 2.'[1, Article X 1.1]

This shows that clinical data is required for demonstrating the device's intended purpose and methods of use, and that this data may be obtained from a review of the literature or from a clinical investigation. Therefore, a literature review is considered to be acceptable as clinical evidence.

According to MEDDEV 2.7/1 revision 4, the clinical evaluation is used to:

- identify data needed for market access;
- define the safety and performance levels needed;
- determine equivalence with other devices;
- identify if a clinical investigation is needed;
- demonstrate conformity with the ERs (safety, performance, and benefit-risk balance acceptability);
- identify what needs to be included in PMS;
- identify if PMCF studies are required.[442, p.10-11]

This shows that the use of other devices deemed equivalent to the device being assessed are allowed as predicates. It also shows that data obtained from a review of the literature on the device in question or a predicate (an equivalent device) is deemed acceptable as clinical evidence. Furthermore, it clearly indicates that clinical investigations are not considered necessary unless it is the only way of providing sufficient clinical data to support claims of conformity.

Table 10.11. Definitions of clinical data, evaluation, investigation, and effectiveness

Definitions	MDD as amended*	MDR (Regulation (EU) 2017/745, Article 2)	GHTF/IMDRF (Source: IMDRF MDCE WG/N56FINAL:2019, formerly GHTF/SG5/N2R8:2007)	MEDDEV 2.7/1 revision 4
Clinical data	(k) '**clinical data'** means the safety and/or performance information that is generated from the use of a device. Clinical data are sourced from: — clinical investigation(s) of the device concerned; or — clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated; or — published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated;	(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;	**Clinical Data:** Safety, clinical performance and/or effectiveness information that is generated from the clinical use of a medical device. **Clinical Evidence:** The clinical data and its evaluation pertaining to a medical device.	**Clinical data:** the safety and/or performance information that is generated from the clinical use of a device. Clinical data are sourced from: - clinical investigation(s) of the device concerned; or - clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated; or - published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated. [derived from Article 1.2.k MDD and Art. 1.2.k AIMDD] **Clinical evidence:** the clinical data and the clinical evaluation report pertaining to a

				medical device. [GHTF SG5/N2R8:2007]
Clinical evaluation	Not defined, but stated in Annex X: *'1.1. As a general rule, confirmation of conformity with the requirements concerning the characteristics and performances referred to in Sections 1 and 3 of Annex I under the normal conditions of use of the device and the evaluation of the undesirable side-effects must be based on clinical data in particular in the case of implantable devices and devices in Class III. Taking account of any relevant harmonized standards, where appropriate, the adequacy of the clinical data must be based on: 1.1.1. either a compilation of the relevant scientific literature currently available on the intended purpose of the device and the techniques employed as well as, if appropriate, a written report containing a critical evaluation*	(44) '**clinical evaluation'** means a systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer;	**Clinical Evaluation:** A set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety, clinical performance and/or effectiveness of the device when used as intended by the manufacturer.	**Clinical evaluation:** a methodologically sound ongoing procedure to collect, appraise and analyse clinical data pertaining to a medical device and to evaluate whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer's Instructions for Use. Note: In exceptional cases where an instruction for use is not required, the collection, analysis and assessment are conducted taking into account generally recognised modalities of use.

	of this compilation; 1.1.2. or the results of all the clinical investigations made, including those carried out in conformity with Section 2.'[1, Article X 1.1]			
Clinical investigation	Also not defined, but also in Annex X it states: 2.3. Methods 2.3.1. Clinical investigations must be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute the manufacturer's claims for the device; these investigations must include an adequate number of observations to guarantee the scientific validity of the conclusions.	(45) '**clinical investigation'** means any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device; (47) '**clinical investigation plan'** means a document that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of a clinical investigation;	**Clinical Investigation:** Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety, clinical performance and/or effectiveness of a medical device. **Clinical Investigation Plan:** Document that states the rationale, objectives, design and pre-specified analyses, methodology, monitoring, conduct and record-keeping of the clinical investigation.	**Clinical investigation:** systematic investigation in one or more human subjects, undertaken to assess the safety or performance of a medical device. Note: 'clinical trial' or ' clinical study' are synonymous with ' clinical investigation'. [EN ISO 14155:2011] **Clinical investigation plan:** document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation. [EN ISO 14155:2011]
Clinical effectiveness or clinical benefit	Not defined	'**clinical benefit'** means the positive impact of a device on the health of an individual, expressed in terms of a meaningful,	**Effectiveness:** The ability of a medical device to achieve clinically meaningful outcome(s) in its intended use as claimed by the manufacturer.	

		measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health;		
Performance	Not defined	(22)'**performance'** means the ability of a device to achieve its intended purpose as stated by the manufacturer;	**Clinical Performance:** The ability of a medical device to achieve its intended clinical purpose as claimed by the manufacturer.	**Clinical performance**: behaviour of a medical device or response of the subject(s) to that medical device in relation to its intended use, when correctly applied to appropriate subject(s). [EN ISO 14155:2011]
Benefit-risk	As a general rule, confirmation of conformity with the requirements concerning the characteristics and performances referred to in Sections 1 and 3 of Annex I, under the normal conditions of use of the device, and the evaluation of the side-effects and of the acceptability of the benefit/risk ratio referred to in Section 6 of Annex I, must be based on clinical data.(MDD Annex X (1.1))	**Benefit-risk determination**-means the analysis of all assessments of benefit and risk of possible relevance for the use of the device for the intended purpose, when used in accordance with the intended purpose given by the manufacturer;(Article 22)	**Safety:** Acceptability of risks as weighed against benefits, when using the medical device according to the manufacturer's labelling.	Benefits and risks should be specified, e.g. as to their nature, probability, extent, duration and frequency. Core issues are the proper determination of the benefit/risk profile in the intended target groups and medical indications, and demonstration of acceptability of that profile based on current knowledge/ the state of the art in the medical fields concerned. p.9
Adverse event	Not explicitly defined	**Adverse event**-means any untoward medical occurrence, unintended disease or	**Adverse Event:** Any untoward medical occurrence in patients/subjects, users or	**Serious adverse event:** adverse event that a) led to death,

		injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device;(Article 3)	other persons. In the context of clinical investigation, for patients/subjects, this would include all untoward medical occurrences, whether or not related to the investigational device, that occurred in the course of the investigation. In the context of clinical experience, this would only include untoward medical occurrences that may be related to the medical device	b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to foetal distress, foetal death or a congenital abnormality or birth defect. NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP [Clinical Investigation Plan], without serious deterioration in health, is not considered a serious adverse event. [EN ISO 14155:2011]
**The MDD as originally enacted did not contain definitions for any of these terms*				

10.2.6.3. Conducting a clinical evaluation

MEDDEV 2.7/1 revision 4 states that '*Clinical evaluation is a methodologically sound ongoing procedure to collect, appraise and analyse clinical data pertaining to a medical device and to analyse whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer's instructions for use.*'[442, p.9]

'*Benefits and risks should be specified, e.g. as to their nature, probability, extent, duration and frequency. Core issues are the proper determination of the benefit/risk profile in the intended target groups and medical indications, and demonstration of acceptability of that profile based on current knowledge/the state of the art in the medical fields concerned.*'[442, p.9]

Additionally, if the demonstration of conformity with the essential requirements is not based on clinical data, then this must be justified and the justification included in the clinical evaluation report (CER); a CER is still required even if it is only to justify the lack of clinical evidence. Although this is likely to only apply to Class I devices, it does show that the CE marking does not guarantee that there is clinical data on the device.

In order to demonstrate compliance with the essential requirements (ERs), the clinical evaluation must '*follow defined and methodologically sound procedures as described in: - Annex X of MDD',*[442, p.9 (emphasis added)] which shows that manufacturers are expected to use study designs appropriate for answering the research question related to determining the safety, performance, and acceptable risk-benefit balance for the device. Manufacturers must present clinical data in a CER[i] to support claims for the device regarding the validity and/or appropriateness of:

- the intended purpose;
- the clinical performance and benefits;
- the measures taken to avoid and/or mitigate risks;
- the usability of the device and suitability of the information materials of the intended users;
- the instructions for use (and promotional materials) for the target population.

[i] More recently, MDCG 2020-13 provides a clinical assessment report template to be used by manufacturers for reporting their clinical evaluation that makes for a more directed and systematic recording and reporting of the clinical evaluation process, which also makes it easier for evaluators to see what they have and haven't done and where the weaknesses lie.
However, it is only a guideline and MDCG guides, similar to the MEDDEVS, are not legally binding, so manufacturers may choose not to use them if they wish, although NBs will likely expect such choices to be explicitly justified.

This does not require demonstration that the device is clinically effective for a particular condition, since 'benefits', according to the MDR, may be '*outcome(s) related to diagnosis, or a positive impact on patient management or public health*'[3, Article 2(53)]

A clinical evaluation must take into account all clinical data, including data obtained from the literature and data held by the manufacturer (including on clinical investigations, which suggests that this is not the usual or only source of clinical data held by manufacturers). IMDRF guidance suggests that clinical data includes '*clinical experience data*',[443, p.13] which must also be included in a CER. Clinical experience data is defined as types of clinical data generated by clinical use of the device in question or similar devices outside of clinical investigations. This clinical experience data may be obtained from: '*post market surveillance reports, registries or medical records (which may contain unpublished long term safety, clinical performance and/or effectiveness data); adverse events databases (held by either the manufacturer or regulatory authorities); and details of clinically relevant field corrective actions (e.g. recalls, notifications, hazard alerts).*'[443, p.13-14] The guidance suggests that this data provides '*real world experience*', with evidence of safety outcomes resulting from normal use, in usual clinical settings, by a wider range of users, who tend to be less skilled or less well trained in the particular device than are those involved in using them in the context of a clinical trial. It is also useful for detecting less common, more serious AMDEs and for demonstrating the end-user 'learning-curve'.

The recommended approach to conducting a clinical evaluation is shown in Figure 11.4.

However, clinical evaluation is intended to be an ongoing (lifecycle) process, used for guiding the pre-market, placing-on-market (i.e. CE marking), and post-market phases of the device. Therefore, the CER, which is an element of the technical file contained within the QMS, must be updated at regular intervals, the frequency of which must be defined and justified, and depends on: the novelty of the device or its components; the level of risk of the device; changes and technological progress or increased understanding of the clinical condition, the device, or alternative treatments; the level of certainty or confidence in the evidence; design or manufacturing changes; and the level of uncertainty regarding longer term clinical outcomes. The CER must be updated annually for high-risk devices, and sooner if the PMS identifies any changes in AMDE risk profiles or trends that impact on the evaluation and conformity of the device's safety, performance or risk-benefit balance.

Table 10.12. Some guidance documents on clinical evidence for medical devices

Document ID	Document Title
Guidance on clinical evaluation	
MEDDEV 2.7.1.Rev4	Clinical Evaluation: A Guide for Manufacturers and Notified Bodies under Directives 93/42/EEC and 90/385/EEC
NBOG 2010-1	Checklist for audit of Notified Body's review of Clinical Data/Clinical Evaluation
IMDRF MDCE WG/N56FINAL:2019 (formerly GHTF/SG5/N2R8:2007)	Clinical Evaluation
imdrf-tech-191010-mdce-n55	Clinical Evidence - Key Definitions and Concepts
MDCG 2020-13	**Clinical evaluation assessment report template**
MDCG 2020-6	Guidance on sufficient **clinical evidence for legacy devices**
Background note	on the relationship between MDCG 2020-6 and MEDDEV 2.7/1 rev.4 on clinical evaluation
MDCG 2020-5	Guidance on **clinical evaluation – Equivalence**
MDCG 2019-9 – R ev.1	**Summary of safety and clinical performance**
Guidance on clinical investigations	
I.S.ENISO 14155-2020	Clinical investigation of medical devices for human subjects - Good clinical practice (ISO 14155:2020)
MEDDEV 2.7/4	Guidelines on clinical investigations: A guide for manufacturers and notified bodies
MDCG 2020-10/1	Guidance on safety reporting in clinical investigations
MDCG 2020-10/2	Appendix: Clinical investigation summary safety report form
MEDDEV 2.7/3 revision 3	Clinical Investigations: Serious Adverse Event Reporting under Directives 90/385/EEC and 93/42/EEC.
imdrf-tech-191010-mdce-n57	Clinical Investigation
MDCG 2024-3	Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices
MDCG 2024-3 Appendix A	Clinical Investigation Plan Synopsis Template
MDCG 2023-7	Guidance on exemptions from the requirements to perform clinical investigations pursuant to Article 61(4)-(6) MDR and on 'sufficient levels of access' to data needed to justify claims of equivalence
2023/C 163/06	Commission Guidance on the content and structure of the summary of the clinical investigation report
MDCG 2021-28	**Substantial modification** of clinical investigation under Medical Device Regulation
MDCG 2021-20	Instructions for **generating CIV-ID** for MDR Clinical Investigations
MDCG 2021-8	Clinical investigation **application/notification documents**
MDCG 2021-6 - Rev.1	Regulation (EU) 2017/745 – **Questions & Answers** regarding **clinical investigation**
MDCG 2020-10/1 Rev.1	Guidance on **safety reporting** in clinical investigations
MDCG 2020-10/2 Rev. 1	Appendix: Clinical investigation summary **safety report form**
Guidance on post-market safety requirements	
Post-market Surveillance (PMS)	
MDCG 2022-21	Guidance on Periodic Safety Update Report (PSUR) according to Regulation (EU) 2017/745
Vigilance (incident reporting)	
MEDDEV 2.12-1 Rev8	Guidelines on a Medical Devices Vigilance System
Ares(2019)4431340 - 10/07/2019	Additional Guidance Regarding the Vigilance System as outlined in MEDDEV 2.12-1 rev. 8

Ares(2018)5672027 - 06/11/2018	Manufacturer's Periodic Summary Report (PSR) Medical Devices Vigilance System (MEDDEV 2.12/1 rev 7)
Ares(2018)5672027 - 06/11/2018	Report Form Manufacturer's Trend Report Medical Devices Vigilance System (MEDDEV 2.12/1 rev 7)
imdrf-tech-170921-pms-ncar-n14-r2	Medical Devices: Post-Market Surveillance: National Competent Authority Report Exchange Criteria and Report Form.
MDCG 2024-1 - Device Specific Vigilance Guidance (DSVG) Template - January 2024	News announcement
MDCG 2024-1	Device Specific Vigilance Guidance (DSVG) Template
MDCG 2024-1-1	DSVG 01 on Cardiac ablation
MDCG 2024-1-2	DSVG 02 on Coronary stents
MDCG 2024-1-3	DSVG 03 on Cardiac implantable electronic devices (CIEDs)
MDCG 2024-1-4	DSVG 04 on Breast implants
MDCG 2023-3	Questions and Answers on vigilance terms and concepts as outlined in the Regulation (EU) 2017/745 on medical devices
Post-market clinical follow-up (PMCF)	
MEDDEV 2.12/2 Rev2	Post Market Clinical Follow-Up Studies: A Guide for Manufacturers and Notified Bodies
MDCG 2020-8	Guidance on **PMCF evaluation report** template
MDCG 2020-7	Guidance on **PMCF plan** template
Note: Generally, the MEDDEVs were applicable under the MDD, and though some may still apply, others no longer apply under the MDR or have been updated as MDCG Guidance. For example, MEDDEV 2.12-1 rev 8 does not apply under the MDR. IMDRF/GHTF guidance only apply where they are specifically referenced by current versions of the MEDDEVs/MDCGs.	

The determination of an acceptable benefit-risk balance appears to be dependent on the 'state of the art' and what is currently considered to be an acceptable risk profile. The literature is one source of evidence determining what is the state of the art and what is considered to be an acceptable safety profile for a particular type of device (in a particular patient group). It includes reports on adverse event profiles for a particular device or device type/category. This means that authors' conclusions regarding the reasonableness or acceptability of the AMDE's observed in their study, and their rates of occurrence, influence the perception of what is considered to be an acceptable level of safety and risk. However, such reports generally don't ask patients their opinions regarding the acceptability of these complications.

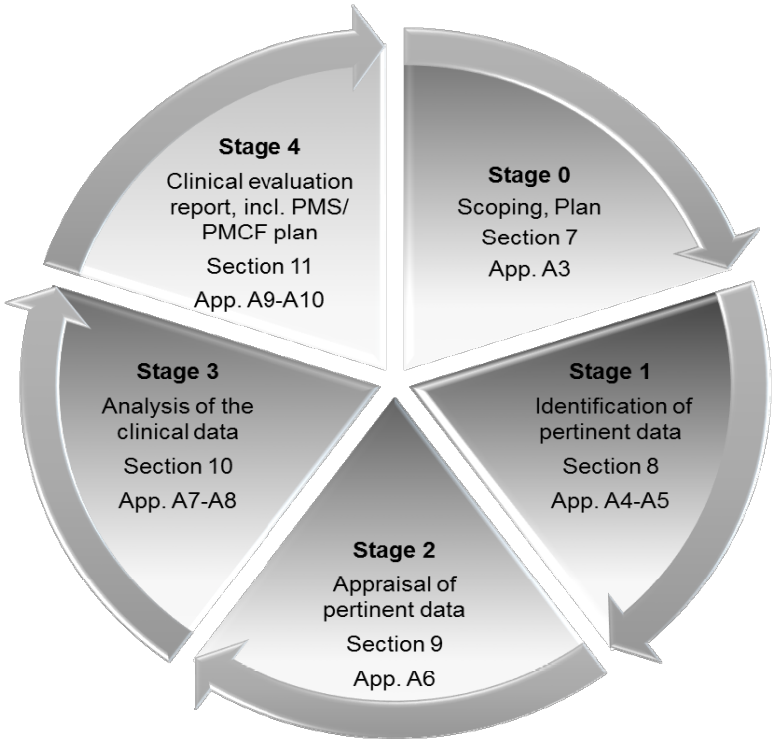


Figure 10.4. Extracted from MEDDEV 2.7/1 revision 4, this figure shows the recommended stages for conducting a clinical evaluation[i]

10.2.7. Clinical evidence requirements under the MDR

In Annex I, the MDR states that devices 'shall be safe and effective', but also that they 'shall achieve the performances intended by their manufacturer'. These two concepts are not the same thing, since a device may perform as intended but still not produce the desired clinical effects.

The MDR does not provide a definition for the concept of 'safe', this must be inferred from Annex I, which states that 'The requirement in this Annex to reduce risks as far as possible means the reduction of risks as far as possible without adversely affecting the benefit-risk ration.' Nevertheless, the MDR provides the definitions listed previously in Table 11.13. It shows that the definitions are similar, but expanded with more detail.

10.2.7.1. Clinical data

Clinical data is information regarding 'safety or performance that is 'generated from the use of the device', which does not necessarily mean a clinical trial. Clinical experience data would still count as clinical data. Neither does it require clinical data 'concerning' effectiveness, just performance. Additionally, the MDR accepts the same kinds of data as the MDD – data on the actual device or on a predicate, and findings from the literature on the device itself or on a predicate (or several predicates).

[i] *Note: 'App.' refers to the Appendices where further guidance is provided on these stages.*

10.2.7.2. Clinical evaluation

The clinical evaluation must be planned and continuously updated '*to verify the safety and performance, including clinical benefits*'. This isn't substantively different to clinical evaluation under the MDD. However, the MDCG has produced five guides regarding clinical evaluation: MDCG 2019-9 – Rev1, MDCG 2020-5, MDCG 2020-6, Background note to MDCG 2020-6, and MDCG 2020-13 (listed in Table 11.13).

The background note explains that Appendix 1 of MCG 2020-6 lists those aspects of MEDDEV 2.7/1 revision 4 that still apply, these are listed in Box 10.4, because they illustrate that much of the previous guidance did not need to be changed, because the MDR made little difference to the aspects they covered. Furthermore, MDCG 2020-6 does not place any requirements on manufacturers to determine the clinical effectiveness of their device

The identified sections of MEDDEV 2.7/1 rev. 4 are considered relevant to MDR as they contain helpful information regarding how to perform activities associated with clinical evaluation:

- 6.4. Who should perform the clinical evaluation?
- 8. Identification of pertinent data (Stage 1)
- 9. Appraisal of pertinent data (Stage 2)
- 10. Analysis of the clinical data (Stage 3). This chapter includes references to the MDD, MDR requirements should be used instead
- A3. Device description - typical contents
- A4. Sources of literature
- A5. Literature search and literature review protocol, key elements
- A6. Appraisal of clinical data - examples of studies that lack scientific validity for demonstration of adequate clinical performance and/or clinical safety
- A7.2. Conformity assessment with requirement on acceptable benefit/risk profile
- A7.3. Conformity assessment with requirement on performance
- A7.4. Conformity assessment with requirements on acceptability of undesirable side-effects
- A10. Proposed checklist for the release of the clinical evaluation report.

Box 10.3. List of MEDDEV 2.7/1 rev.4 sections that are still applicable to clinical evaluation under the MDR, according to MDCG 2020-6

10.2.8. Clinical investigations

There are MEDDEVs for reporting adverse events during clinical investigations, and there is a MEDDEV for guiding clinical evaluations, but this was not located. Therefore, I had to draw on the IMDRF guidance for this.

The recommendations are explicit in the elements to be included in the design of a study and, if applied, should provide the necessary evidence. They also recommend that clinical investigators use the ISO 14155 to guide the conduct of clinical investigations.[444, p.10] The guidance claims that '*A properly conducted clinical investigation, including compliance to the clinical investigation plan and local laws and regulations, ensures the protection of human subjects, the integrity of the data and that the data obtained is*

acceptable for the purpose of demonstrating conformity to the Essential Principles.'[444, p.10]

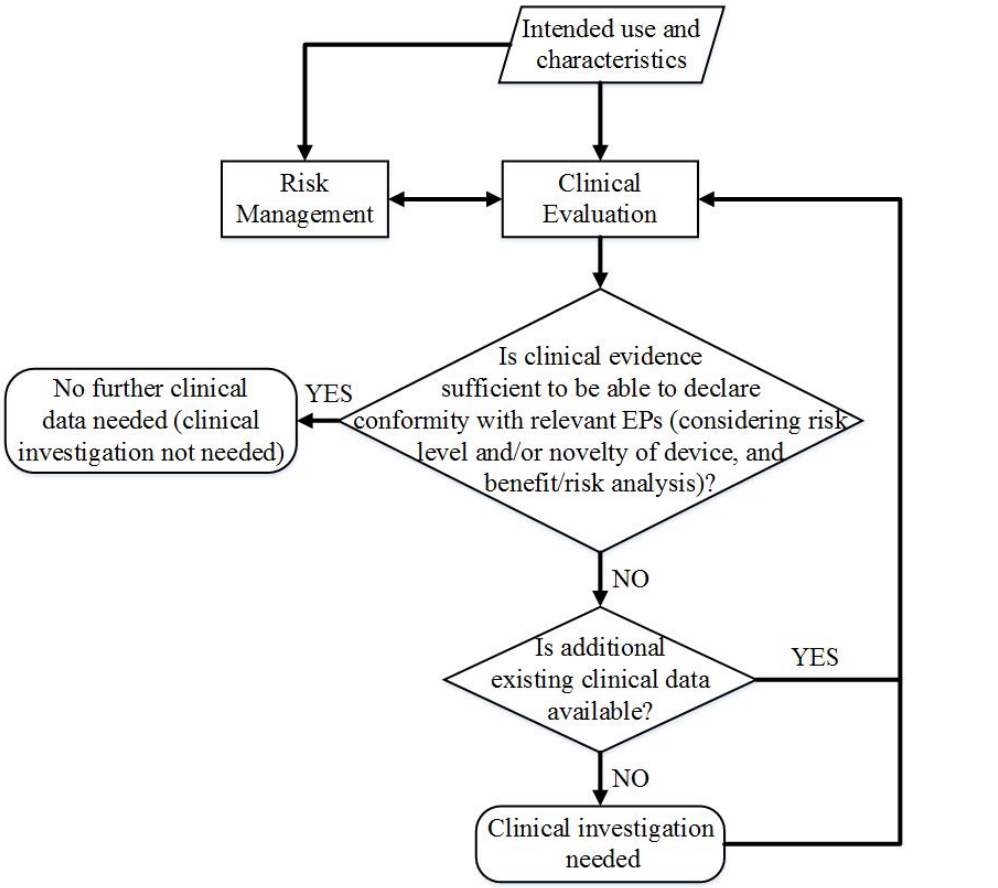


Figure 10.5. Extract from IMDRF guidance on Clinical Investigation[i]

However, the guidance also states that '*The design of the clinical investigation, including the study objectives and statistical considerations, should provide the clinical data necessary to address the residual risks, including aspects of clinical performance*'. This means that the study is primarily to be conducted for addressing the ERs, which don't explicitly include a requirement for evidence of clinical effectiveness. Therefore, it is unlikely that clinical effectiveness is the research question being investigated for most medical device clinical investigations. This calls into question whether clinical investigations on medical devices with unknown efficacy are actually compliant with the declaration of Helsinki when they are not investigating efficacy or effectiveness.

Furthermore, it is very clear that the conduct of clinical investigations is discouraged, instead manufacturers are encouraged to utilise clinical evidence from other sources,

[i] Document reference: IMDRF MDCE WG/N57FINAL:2019 (formerly GHTF/SG5/N3:2010)

such as those described above. This is clear from Figure 11.5, which is a decision aid provided by IMDRF to decide if a clinical investigation is needed.

10.2.8.1. Clinical investigations under the MDR

The requirements placed on clinical investigations by the MDR are substantially more detailed than in the MDD. The manufacturer, the study sponsor, must submit a detailed application form to the NCA for assessment of the clinical investigation plan (CIP), and submit the CIP to the relevant national research ethics committee (REC) for review. To gain approval for the clinical investigation the investigation must receive approval (or at least not receive a negative opinion) from the REC, and authorisation to conduct the investigation from the NCA.

The MDR describes detailed requirements it imposes on the sponsors (and investigators) for conducting and submitting applications for clinical investigations on medical devices. Much of this relates to the study design (although it does not mandate RCTs) and the consent process, particularly the methods to be used in obtaining consent from specific vulnerable groups. Importantly, the MDR requires that the investigator(s) adhere to the CIP or explain any deviations that occur. Whilst the CIP will not be publicly available, a summary of its contents will be available in the clinical investigation report (CIR), which the MDR also requires.

The CIR and its summary are to be uploaded to EUDAMED. Subjects are to be informed to '*the extent possible'*,[3 Article 63(6)] when these have been uploaded. It is intended that the CIR and its summary are to be made available within a year of the conclusion of the clinical investigation (or by three months if it has been terminated early or halted temporarily), but this is not mandated '*where, for scientific reasons, it is not possible to submit the clinical investigation report within one year of the end of the investigation*', then it is to be submitted as soon as possible and the planned date for when it is to become available is to be included in the CIP, and justified.[3 Article 77(5)] Furthermore, the CIR and its summary are (eventually) to be made publicly available via EUDAMED.

This is a major improvement in terms of the transparency of the evidence, since the CIR is to include the investigation's objective, methods, results, a summary of the adverse events experienced by participants, and a discussion and conclusion on the results, as well as a description of the investigated device and its intended purpose.[3 Annex XV(7)] The details that are required to be presented in the CIR and its summary are listed in Boxes 10.5-10.6.

However, there is a slight caveat to this optimism. The MDR does not specify or require that clinical investigations be conducted to determine the clinical efficacy or effectiveness of the device, instead this is left to the interpretation of ethical principles as set out in the

Declaration of Helsinki, which it does require investigators to adhere to. However, the CIR does not have to address this question of effectiveness, instead it is to describe the clinical benefits, though these may not translate into long-term clinical effectiveness. Additionally, it is the sponsor who is responsible for preparing the CIR. The sponsor is not the investigator, but the funder of the investigation, which represents a distinct conflict of interest. Furthermore, it is not unknown for funders to only report evidence that is favourable to them, and whilst the report must be signed off by the investigators, they are not without their own conflicts of interest when the sponsor is funding their research.

Specifically, the CIR must address the following points:

Background

Investigation title, study registration number, CIP number, and identification details for the study investigators at each investigation site

Methods

- purpose and research objectives
- completion date, and, where relevant, details of early termination, temporary halts or suspensions
- study design, ethical aspects, and monitoring and quality measures
- target patient populations
- selection criteria
- sample size and sample size calculation
- treatment schedules
- concomitant treatments
- follow-up duration
- statistical plan, including hypothesis and analysis methods, and justification

Results

Results of the clinical investigation covering, with rationale and justification:

- participant demographics
- analysis of results related to:
    - chosen endpoints
    - details of subgroup analysis, as well as compliance with the CIP
    - follow-up of missing data, withdrawals, and losses to follow-up
    - summary of SAEs, AMDEs, device deficiencies and any relevant corrective actions

Discussion & Conclusions regarding the following:

- safety and performance results
- assessment of risks and clinical benefits
- discussion of clinical relevance in accordance with clinical state of the art
- any specific precautions for specific patient populations
- implications for the investigational device
- limitations of the investigation

Box 10.4. Contents of the Clinical Investigation Report (CIR)

The CIR Summary is to be written in readily understandable language and include the details listed in Box.5. The application to conduct a clinical investigation, detailed in Annex XV Chapter II, must include the following**:**

1. Application form
2. Investigator's brochure
3. Clinical investigation plan (CIP)
4. Other information
    - statement that the device conforms to the GSPR apart from the aspects under investigation, and that every precaution has been taken to safeguard subject for those aspects
    - REC opinion
    - proof of insurance/indemnity
    - patient information leaflet (PIL), consent form and any other relevant documents used for the consent process
    - data protection measures
    - full details of the technical documentation (elements of which are to be made available on request to the NCA assessing application)

CIR Summary contents:

- title
- purpose
- description of the investigation
- investigational design
- methods used
- results
- conclusion
- completion date
- details of early termination, temporary halts or suspensions

Box 10.5. Contents to be included in the CIR Summary report

MDCG guidance and device effectiveness

The requirements are detailed, but in the relevant MDCG guidance there is a the lack of guidance for assessing device effectiveness as there are only two mentions of effectiveness. Regarding the study's aims and hypothesis MDCG 2024-3 (p.11) states that: The purpose of the clinical investigation, claims for clinical performance, effectiveness or safety of the investigational device that are to be verified should be described, whilst MDCG 2021-8 defines usability as 'the characteristic of the user interface that establishes effectiveness, efficiency, ease of user learning and user satisfaction in the intended use environment (section 3.16). Though it is not precluded, there is no explicit guidance or requirement to demonstrate the clinical effectiveness of a device in an RCT. None of the other MDCG guidance documents listed in Table 10.13 mention clinical efficacy/effectiveness.

10.2.9. Post-market surveillance and vigilance

10.2.9.1. Post-market surveillance

Under the MDD, manufacturers were expected to have a PMS system in place as they had to submit an undertaking '*to institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase'* to their NB as part of their application for assessment of conformity (under Annexes II, V, and VI). However, the original MDD did not specify any details regarding what to include or how to implement this system. Following amendment,[374] manufacturers were expected to develop a PMS plan and a post-market clinical follow-up (PMCF) plan, which together with the data from PMS was to be used to update the clinical evaluation for the device, but still very few details were specified.

The MDR rectified this by clarifying these requirements in Article 61(11) and Articles 83-100, and providing details on the required documentation for PMS in Annex III. Under the MDR, the manufacturer must institute a systematic process for PMS, including a PMS plan (Article 84). They must prepare a periodic safety update report (PSUR) for each device and each category or group of devices *'summarising the results and conclusions of the analysis of post-market surveillance data … with a rationale and description of any preventive and corrective actions taken*.' (Article 86(1))

Annex III details the requirements for the documentation to be presented as part of the PMS technical documentation assessed by their NB must include the manufacturer's PMS plan, their PMCF plan (or a justification why this is not needed), and the PSUR (or a post-market surveillance report in the case of Class I devices).[3 Annex III] However, the PMS plan is to focus primarily on acquiring information on incidents, AMDEs, complaints, and feedback from users/distributors/importers. Although, manufacturers are also required to review data from the literature, databases, and/or registers, as well as publicly available data on similar devices, which could conceivably include data on efficacy (though this is unlikely given that it largely isn't being required by the regulators, healthcare systems, or healthcare professionals). Nevertheless, the plan should be to gather any information previously mentioned to allow: the device's performance to be 'characterised'; comparisons to be made with other devices; and reassessment of the benefit/risk balance and the risk management process. It should also include a description of the methods and processes being used to: assess the collected data; investigate complaints; analyse 'market experience'; identify changes in incident trends (frequency or severity) and determine their statistical significance; identify when and what corrective actions to take; and communicate effectively with the regulatory authorities, users, and economic operators.

The PMS plan is the manufacturer's proof of compliance with the requirement regarding a PMS system and the obligations detailed in Article 83, which include that manufacturers actively and systematically gather, record, analyse, and draw conclusions on the quality, performance, and safety of their device(s), and determine, implement, and monitor any necessary preventive and corrective actions arising out of their analysis.[3] Article 83(2) The data and its analysis is to be used to update the benefit-risk determination, the design and manufacturing information, the IFU and labelling, the clinical evaluation, and the SSCP. It is also intended to identify any need for CAPA or FSCAs, incident trends and any changes in these that require reporting, and possibilities for improving their device (usability, safety, or performance) and its risk management.

10.2.9.2. Vigilance

Vigilance generally refers to incident reporting, with manufacturers being mandated under the MDD/MDR to report serious incidents to their CA if there is:

'(i) any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the instructions for use which might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health;

(ii) any technical or medical reason connected with the characteristics or performance of a device leading for the reasons referred to in subparagraph (i) to systematic recall of devices of the same type by the manufacturer.'(REF)((MDD, Art. X; MDR, Art. X)

Further complicating interpretation is the need to judge whether an incident is serious one or not. MEDDEV 2-12.1 rev 8 gives examples of serious incidents, as detailed in Table 10.13, and suggests that a serious deterioration in someone's state of health can include a life-threatening injury, permanent physical damage or functional impairment, effects inducing medical/surgical intervention to prevent life-threatening injury or permanent harm, any harms related to an incorrect diagnosis/test result, or damage to the unborn, amongst others.[445]

MEDDEV 2.12 revision 8 also provides guidance of what *not* to report. However, these reporting exemptions represent a lost opportunity to improve patient safety, since they still represent important safety issues. For example, if the fault/risk is detected before the device is used in one instance but this is not reported, means that others cannot learn from it, and the next time such a fault occurs it may be missed by the user, causing avoidable patient harm.

Further, a serious risk of harm that results from the use of a device but where the cause is considered to be the patient's condition misses a valuable opportunity for learning. It may be that it is the interaction between the patient's condition and the device that results in the harm and not simply as a direct result of the patient's condition. This means that

the device may be contraindicated in some sub-groups of patients (and conversely, that it may be more suitable for others). It also means that the risk of a serious harm occurring needs to be included in the pre-operative consent discussion to allow the patient to consider if they are prepared to take that risk and give informed consent if they do.

Not reporting a serious injury because the cause is attributed to using a device after its 'best before' date means that users may not realise the risks of ignoring, or not knowing, the device's expiry date. This is less of a problem where the device is a piece of equipment, aid or appliance, where the information should be clearly displayed and the risk of injury more visibly obvious, but it may be a significant problem for devices that are too small for this information to be clearly visible on the device, such as small implantable devices. It is also a problem in contexts where such dates may be ignored due to a supply shortage, such as in low-income countries.

Also, where a protection engineered into the device prevents a serious incident from occurring there should be no incident to report. However, it would still be beneficial for users of such devices to know that a failure in this preventive mechanism would be likely to result in harm, so that they know not to use the device if they are suspicious that the preventive mechanisms has or is likely to fail.

To not report a serious incident just because it is expected and foreseeable doesn't make it any less serious to the patient involved, and by not reporting it means that it is impossible to accurately assess the frequency or severity of these incidents, making trend reporting inaccurate, which means that the information given to patients on the likelihood of such harms occurring is likely to be inaccurate.

Finally, while it is understandable that incidents that are unlikely to have a risk of causing death or serious injury are not reported, such incidents may still be important to patients and clinicians, who are likely to want to make informed choices and decisions about all major and 'minor' risks involved.

The original MDD envisaged a central system for collecting vigilance and market surveillance data to support the monitoring of medical device safety. Following amendment, the European databank for medical devices was established through Article 14(a) as a central repository for serious incident reports, as well as data on clinical investigations, certificates issued by NBs, and the registration of certain economic operators. None of this data was made publicly available. With the MDR, the functionality of this databank is being expanded and some of the information will be made publicly available. The main advantage of this is that it allows the CAs to more effectively perform market surveillance and detect poorly performing devices sooner.

The next section describes the evolution and contents of this system.

Table 10.13. MEDDEV 2.12-1 revision 8 guidance on reporting incidents

Reporting required if:
a) life-threatening illness, b) permanent impairment of a body function or permanent damage to a body structure, c) a condition necessitating medical or surgical intervention to prevent a) or b). Examples: - clinically relevant increase in the duration of a surgical procedure, - a condition that requires hospitalisation or significant prolongation of existing hospitalisation. d) any indirect harm (see definition under section 4.11) as a consequence of an incorrect diagnostic or IVD test result or as a consequence of the use of an IVF/ART device when used within MANUFACTURER´s instructions for use (use errors reportable under section 5.1.5.1 must also be considered). e) foetal distress, foetal death or any congenital abnormality or birth defects. However, this is not an exhaustive list.[445]
Reporting is not usually required if:
5.1.3.1 Deficiency of a device found by the user prior to its use 5.1.3.2 Event caused by patient conditions 5.1.3.3 Service life or shelf-life of the medical device exceeded 5.1.3.4 Protection against a fault functioned correctly 5.1.3.5 Expected and foreseeable side effects 5.1.3.6 Negligible likelihood of occurrence of death or serious deterioration in state of health. [445, p.2]

10.2.9.3. European Databank on Medical Devices (Eudamed)

The Medical Device Directives (as amended) collectively required the central collection and analysis of certain types of data, including surveillance and vigilance data, for medical devices. In order to do this the German Institute for Medical Documentation and Information (DIMDI) developed the initial version of the EUropean DAtabank on MEdical Devices (Eudamed) between 1997 and 1999.[446] Intended as a data repository and a secure web portal for information exchange between the MSs and the Commission, Eudamed was an IT system designed to house information on medical devices that received or were refused certification (or had this withdrawn, amended, suspended, or supplemented) following a conformity assessment procedure for CE Marking.[447]

The EU Commission took over responsibility for Eudamed from DIMDI in 2000 under the auspices of the Directorate-General for Enterprise and Industry (DG-ENTR), and NCAs have been able to access the database since 2004. However, development of the database slowed until 2006, when the Commission initiated further work on it.[446] A new version of the software (Eudamed2) was approved in 2009.[446] According to DIMDI, the responsibility for Eudamed moved from the DG-ENTR to the Directorate-General for Health and Consumers in 2010, and then to the Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs (DG-GROW) in 2014.[446] With the new

Commission in 2019 the remit for medical devices moved yet again, this time from the DG-GROW to the Directorate General for Health and Food Safety (DG-Santé).[448]

Data had been entered into Eudamed on a voluntary basis, but with the introduction of the Commission Decision on the European Databank on Medical Devices (Eudamed) (Decision 2010/227/EU) it became a legal requirement that MS enter specified data into the system from the 1 May 2011.[449,450] For devices that were already on the market (i.e. legacy devices) only the data on the manufacturer, the authorised representative, and device registration were required to be entered.[449, Article 5] The date set for completion of entry of legacy data was 30 April 2012.[449, Article 6] The data in Eudamed and Eudamed2 were solely accessible by the actors involved (i.e. the NCAs and the Commission) and its purpose was to meet the requirements of the MDDs, particularly to facilitate market surveillance and vigilance activities.[450] The data has never been made publicly available.

The MDR includes additional requirements for this central vigilance database, requiring Eudamed2 to be further developed to include new data modules. Eudamed2 is still being developed by the Commission, now called EUDAMED, to meet the additional requirements of the MDRs.[447] It is intended to be an interoperable and multifunctional system that includes a registration system, a notification system, and a dissemination system, serving as a means of collaboration and communication of confidential information between the medical device competent authorities. The new data modules will cover the registration of manufacturers and other economic operators responsible for medical devices entering the European market ('Actor registration'); the registration of individual types of devices or/and individual device unique device identifiers (UDI/Devices); the registration of NBs and the certificates that they have issued, revoked, refused, supplemented, or amended (NBs/Certificates); clinical investigations and performance studies (CI/PS); vigilance and post-market surveillance data (PMSV); and market surveillance. Some of this data is, or will be, made available to the public.

One of the stated claims for EUDAMED is that it will *'improve and coordination of information regarding medical devices available on the EU market.'*[447] Despite this, much of the information will not be available to the public. For example, the clinical data upon which certification and CE marking is based will still not be made publicly available.

Initially it was intended that EUDAMED would not be made available until it was fully upgraded and operational. However, as the full implementation of the MDR had to be deferred[i], and because development of the database also required more time, the Commission decided that each of the modules would be made available as soon as it became functional to facilitate compliance with the MDR. The Actor registration module

[i] It had originally been due to come into full force on the 26th of May 2020

(for economic operators) was made available in December 2021, and the modules on UDI/devices and NBs/certificates have since become operational.[451]

By March 2022, EUDAMED contained Actors, Devices, and Certificates modules. The Actors module includes economic operators (including manufacturers, authorised representatives, importers, and system/procedure pack producers), designating authorities, competent authorities, and notified bodies. The Devices module is subdivided into those devices that received their CE marking through the MDD, AIMDD, IVDD, MDR, and the IVDR, and further subdivided by their different risk classes. Table 10.14 summarises some of the data extracted from EUDAMED on the actors and devices.

Table 10.14. Summary of data held in EUDAMED 29th March 2022

Group	Numbers recorded in EUDAMED
Actors	
Manufacturers	12957
Authorised Representatives	1385
Importers	3697
System/procedure packs producers	468
Competent Authorities	64
Notified Bodies	27
Designating Authorities	27
Devices	
MDR Class III	23
MDR Class IIb	423
MDR Class IIa	5,252
MDR Class I	26,386
MDR All classes	32,084
MDD Class III	4456
MDD Class IIb	3519
MDD Class IIa	No records found
MDD Class I	2,178
MDD all classes	No records found, but the above records add up to 10,153
AIMD	14
Total MDR, MDD, & AIMD	**42,251**
Certificates	
Certificates	4

It provides us, for the first time, with an idea[i] of the numbers of manufacturers producing for the EU market (the vast majority of whom are based in China) and the number of devices being placed on the EU market, which is in the region of 42,000.[ii]

The certificates module lists uploaded certificates of conformity assessment and provides access to those certificates. As of 29 March 2022, there were only four certificates on the system, certifying the QMS of four manufacturers and covering in excess of nineteen different devices[iii]. None of the data needed for clinical decision-making is included in these certificates. However, the use of EUDAMED is still not mandatory. Its use only becomes mandatory six months after the notification of this is published in the OJ, and prior to this notification EUDAMED must be fully functional and have been evaluated externally.(Articles 34 and 123(3)(d)) The anticipated timeline for this suggests that the CI/PS module will not be operational until Autumn of 2026, and its use will not be mandatory until the end of 2027.

What has been made available from the original Eudamed database is an annual summary of the National Competent Authority Report (NCAR) statistics, which are used to examine AMDEs as an indicator of medical device safety in the next Section.

Use of EUDAMED is increasing. As of 18 April 2024, across all CAPs for the MDR and IVDR, there are 442 certificates registered in EUDAMED. Table 10.15 lists those issued under the MDR. There are 325 EU Quality Management System Certificate certificates (Annex IX Chapter I) (244 issued; 49 supplements; 25 amended; 1 restricted; 0 suspended; 2 withdrawn; 2 cancelled by the manufacturer; 0 reinstated; and 2 reissued) and 1 listed as refused, although this latter one is mistakenly listed under this Annex as it is also (correctly) listed under Annex XI Part A.

Table 10.15. Certificates issued under the MDR registered in EUDAMED 18th April 2024

MDR Annex	Certificate	No. of certificates
IX, Chapter I	EU Quality Management System Certificate	325
IX, Chapter II	EU Technical Documentation Assessment Certificate	34
X	EU Type-Examination Certificate	2
XI, Part A	EU Quality Assurance Certificate	37 & 1 refused
XI, Part B	Eu Product Verification Certificate	6

10.2.9.4. Information to be made available to the public under the MDR

It is not always clear what information is to be made publicly available, but Box 10.6 lists the information that, according to the MDR, should be available to the public. The most

[i] Albeit an incomplete picture since registration is not yet mandatory.

[ii] Excluding in-vitro diagnostic devices. EUDAMED didn't provide data on the number of Class IIa devices, making it impossible to give an exact number, but this may just have been a system blip, and the data may be available at another time

[iii] The exact number of different types of devices covered by each certificate is not specified.

Information to be made available to the public under the MDR

- Core data elements in the UDI database, which mostly refer to identification data (regarding the device, manufacturer, and AR), but does not include any clinical data (unless contraindications and critical warnings are considered to be clinical data).[3 Article 28(3)]
- A summary of the report on the monitoring and on-site audits of the NBs and any subsidiaries/sub-contractors by the MS.[3 Article 44(12)]
- Name and address of health institutions manufacturing in-house devices, device identification details, and a declaration stating that the device(s) meets the GSPR and providing justification and details on any GSPR not fully met.[3 Article 5(e)]
- General information on how MS assess, designate and notify CABs, monitor NBs, and changes impacting these activities.[3 Article 35(7)]
- The summary of safety and clinical performance (SSCP) for implantable and Class III devices (not custom-made or investigational devices). Clinical information includes a summary of the clinical evaluation (how extensive this will be is as yet unknown), any relevant PMCF information, and possible diagnostic or therapeutic alternatives.
- NBs' list of subsidiaries.[3 Article 37(3)]
- List of NBs, their ID numbers, the CAPs and the types devices they are authorised to assess (available on NANDO).[3 Article 43(2)]
- List of fees charged by NBs.[3 Article 50]
- Information on devices placed on the market, certificates issued by NBs (Article 56(5)), economic operators, and clinical investigations to be available on EUDAMED.[3 Article 33(1)]
- An annual summary report on the activities related to the peer review of DAs.[3 Article 48(4)]
- FSNs issued by the manufacturer.[3 Article 89(8)]
- Summary of MS' review and assessment of the functioning of their market surveillance activities (on a four yearly basis).[3 Article 93(8)]
- Names and affiliations of MDCG members.[3 Article 103(2)(2nd para)]
- Declaration of interests of members of the MDCG, its sub-groups, the expert panels and expert laboratories.[3 Article 106(3)(2nd para)]
- The structure and level of fees to be levied by the MS or their CAs to carry out the tasks of the MDR shall be available on request.[3 Article 111(2)]
- Declarations of interest of the top management level staff in NBs.[3 Annex VII (1.2.6)]
- Description of the certification application procedure by NBs for conformity assessment.[3 Annex VII (4.2)(a)]
- The scientific opinion of the expert panel and, where the NB's opinion diverges, the NB's written justification.[3 Annex IX (5.1)(g)]

Note: 'Information exchanged between Member States shall not be made public where to do so might impair market surveillance activities and co-operation between Member States.'[3 Article 100(3)]

Box 10.6. Information to be made publicly available under the MDR

important of these are the SSCP and the CIR, which should present the clinical data on devices, or at least an understanding of the evidence upon which their CE marking is based.

10.2.9.1. Other sources of safety information

Other potential sources of data on medical device safety include the competent authority websites listing of safety notices, and national or hospital databases. However, each has its own weaknesses. None provide European-wide data.

Competent authority safety alerts

The competent authorities receive (mandatory) safety alerts from manufacturers and voluntary reports of incidents from users. Once the manufacturer has issued a public safety notice, called a Field Safety Notice (FSN), *then* the competent authorities can publish safety notices (SNs) describing the safety issue and what the manufacturer is doing to address it. In Ireland, the HPRA publishes these SNs on its website. The HPRA also compiles and publishes the industry-notified FSNs into a monthly summary.

National databases

There is no national database for medical devices, implantable or otherwise. The HSE keeps an inventory of its medical equipment at the hospital level, which is maintained in order to manage, maintain, and replace equipment as it ages.(KI-01) However, data is not collected on the individual patient outcomes following use or application of the medical equipment. Furthermore, this inventory does not include implantable devices. In fact, there is no national database systematically collecting data on patient outcomes related to implantable devices, with the exception of a small number of implant registries that are collecting data on a specific implant type. The Irish National Orthopaedic Register is an example of such a registry in Ireland, but it only collects data on specific implants – the larger joint prostheses. This data is not available to the public[i].

Registries in other countries

Some countries have established patient registries or implant registries that researchers may access to analyse their data. Some examples of these include registries for specific (usually large) joint prostheses, breast implants, urogynaecological mesh, and cardiac implants.[452–456] These provide a means of market surveillance of specific devices used within their jurisdictions. For example, he National Joint Registry (NJR) in the UK detected the unusually high rate of early failure of metal-on-metal hip implants,[457] and the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) detected the high failure rates of the articular surface replacement (ASR hip) in 2006 leading to its withdrawal from the Australian market.[458] Most of these, however, focus on detecting failing devices earlier in the post-marketing period rather

[i] However, it did publish a report in September 2021, its first, following seven years of data collection, at one site at least.

than detecting problematic devices in the pre-market phase or evaluating their actual efficacy/effectiveness.

The Orthopaedic Data Evaluation Panel (ODEP), initially set up in 2002 to support the implementation of National Institute for Health and Care Excellence (NICE) guidance for hip implants, has established a process for benchmarking major joint implants (e.g. hips, knees, shoulders) regarding the level of evidence available on each implant (based on the data submitted to it by the manufacturers, at least initially) in terms of the number of years of accumulated evidence and the strength of that evidence. This is rated by the panel of experts and they recommend the use of devices that meet the benchmark set by NICE guidance (hip implants that have at least ten years of experience with a revision rate less than 5%. Devices that meet this benchmark and have strong evidence[i] supporting this assessment would be rated as ODEP 10A*[ii]).[459] This allows surgeons and the public to see what devices have long term data on implant survival, however, it provides little data on other outcomes that matter to patients, such as the effects that they have on pain, stiffness, functionality, and complications not resulting in revision.

Patient registries are preferable as these allow comparative assessment of outcomes across different interventions, and some patient registries do exist. One example of this is SWEDEHEART, which is a registry of patients enrolled in Sweden following hospitalisation with acute coronary syndrome or undergoing coronary angiography, angioplasty, or cardiac surgery.[460–462] It collates data on multiple variables to provide a comprehensive individual patient record and allows evaluation of aggregate patient outcomes from a variety of interventions.

Automated data capture systems

Some healthcare systems have also introduced initiatives to automatically capture data, particularly for inventory management, that enables linking of product data to patients, allowing the possibility of evaluating patient outcomes from those products.

One such example is the initiative in the UK, 'scan 4 safety'. The NHS adopted the Scan4Safety stock management tool as part of their Digital Clinical Safety Strategy, to enable the tracking and tracing of medicines, devices, and equipment from inventory stock to the patient.[463] Launched by the Department of Health and Social Care (DHSC) in 2016, it uses barcodes and scanning technology to identify each patient and the

[i] Strong evidence generally means higher numbers of patients (giving greater confidence in the results presented), with all patients being subject to follow-up (their outcomes recorded).

[ii] The number indicates the number of years of experience with the device, the A indicates strong evidence, whereas a B would indicate that the evidence is acceptable, usually with smaller numbers of patients than the A rating (giving less confidence in the results than A), but sufficient data to demonstrate compliance. Having a revision rate less than a 10% in ten years would obtain an A rating, less than 5% is given a star, indicating that the evidence is stronger than that even for A or B.

devices or medications being given to them, which, at least in theory, should reduce the rates of errors, but also allows for traceability and linkage of treatments received to patient outcomes. In 2022, linkage of the data from the Scan4Safety database with The NHS England Outcomes and Registries Programme and the Outcomes Registry Platform began. The Outcomes Registry Platform is being developed by the NHS to consolidate existing implantable device-level registries and unify these into a single registry, as well as to develop additional data collections. It is intended to be a vigilance tool, but could potentially be used in research to link patient outcomes to their devices and/or medications and facilitate clinical outcomes research.

However, this is dependent on having already implemented an electronic health record system, an electronic patient identifier system, and the IT systems required to link and save the data. Unfortunately, although the HSE has already implemented a similar scan and trace system for devices and equipment for stock control and inventory management, Ireland still lacks an electronic healthcare record and patient identifier system, making linkage and patient follow-up impossible.

Hospital In-Patient Enquiry (HIPE)

This database houses information collected from individual patient charts in individual hospitals by HIPE coders. The data is accessible to researchers on special application. Data recorded on HIPE include patient details, information regarding the primary diagnosis that prompted the admission, up to twenty procedures that a patient experienced during that particular episode of hospital care, and the specialties of the consultants involved in that patient's care. It does not provide data linkage between episodes of care, so information is only available on a single episode of care. This means that patients having a device implanted during one episode of care that results in subsequent episodes of care (e.g. due to device faults or failure) cannot be identified as the care episodes can't be linked either to an individual patient or to a particular device.

National Competent Authority Reports (NCARs)

The GHTF collaborated to develop a system of sharing information on serious adverse medical device events (AMDEs) between national competent authorities (NCAs). NCAs share reports on devices that they become concerned about, which the manufacturer(s) has not yet made them aware of. Information considered to be confidential (i.e. not already publicly available) in these NCARs could only be shared between NCAs in the NCAR Exchange Program who had established mutual confidentiality agreements, and who had a single contact person (trained in the exchange criteria and procedures) who agreed to not redistribute the information. The terms and conditions set down for the GHTF NCAR Exchange Program are similar to those established later by the EU

Commission for the EU's NCAR exchange programme.[464–467] The individual NCARs are not publicly available. However, a summary of the EU NCARs is published each year detailing the number of reports shared by participating countries. Whilst the data that they contain is minimal, they are currently the only accessible European-wide data on medical device safety. These are explored in more detail below.

10.3. Outcomes

There is limited data available to investigate the impact of EU regulation on the safety of devices. As described previously, EUDAMED is still under development, and even when complete will only allow limited public access to the data it contains.[447] Only the competent authorities and the Commission will be able to access all the data. However, in time, it should be possible to access the SSCP, summarising the safety and performance evidence available on a device.

Nevertheless, at the time of this research, the only accessible European-wide data on medical device safety were the NCAR summaries, so there were used to assess changes in the patterns in device safety between 2007 and 2019/2020 (the years for which these reports were available). The number of NCARs exchanged between the NCAs may be taken as a crude indicator of the safety of medical devices bearing the CE marking.

This section reviews the impact of the regulatory process on safety by analysing the annual National Competent Authority Reports (NCARs) published by the European Commission and the guidance documents on reporting NCARs provided by the Commission and the IMDRF. Reporting of incidents between NCAs takes the form of National Competent Authority Reports (NCARs). This process is guided at the European level by MEDDEV 2_12_1-rev8 and the additional guidance issued in 2019, and at the global level[i] by GHTF and IMDRF guidance documents[ii].

[i] There are two types of NCARs, with two reporting programmes: the EU NCAR Programme and the IMDRF NCAR Exchange Program, which succeeded the GHTF NCAR Exchange Program. These are related, but different. The EU NCAR Programme is an exchange of NCARs within the EU between NCAs and the Commission, whilst the IMDRF NCAR Exchange Program is an exchange of NCARs between NCAs that are members of the IMDRF NCAR Exchange Program who have also signed a confidentiality agreement with the reporting NCA. This section draws on the data from the EU NCAR Programme, but as it also relies on documentation and guidance produced by the IMDRF and GHTF working groups these are also referred to.

[ii] These have changed over time, the current version is MDRF/NCAR WG/N14 FINAL:2017 (Edition 2) "Medical Devices: Post-Market Surveillance: National Competent Authority Report Exchange Criteria and Report Form". Previous version included IMDRF/NCAR WG/N31 FINAL:2015; GHTF/SG2/N79R11:2009; SG2(PD)/N79R5 (2005), where PD refers to Proposed Document, SG2 refers to Study Group 2, and WG refers to Working Group.

10.3.1. National Competent Authority Reports reporting criteria

The reporting criteria for the exchange of NCARs between the NCAs and the Commission are set out in MEDDEV 2-12.1 rev 8 as set out in Box 12.1.[445] The criteria are that corrective action has been performed or required; there is a serious risk to patients or others' safety; or the manufacturer doesn't provide a timely report.[i]

Information shall be disseminated between National Competent Authorities and copied to the Commission when: A) a FSCA is performed by the MANUFACTURER; B) a National Competent Authority requires the MANUFACTURER to perform an FSCA or to make changes in an FSCA that the MANUFACTURER has already initiated; C) there is a serious risk to the safety of patients or other USERs, but where no corrective action has yet been established, although measures are under consideration; D) the MANUFACTURER does not provide a final report in a timely manner. This information is called National Competent Authority Report (NCAR).

Box 10.7. NCAR reporting criteria based on MEDDEV 2.12-1 rev 8

The guidance is unclear regarding whether all four criteria must be fulfilled, but based on IMDRF guidance it would seem reasonable to assume that NCARs are to be exchanged when one or more of these criteria is fulfilled. However, NCAs are also advised that they:

> *'should use their discretion where corrective action is taken by a MANUFACTURER which is not considered to be essential to protect the safety of patients or other USERs. Under these circumstances a National Competent Authority Report may not be necessary. In cases of doubt there should be a pre-disposition on the part of National Competent Authorities to disseminate the NCAR.*'[445]

Thus, not all FSCAs are communicated via NCARs, and there is room for judgement regarding whether to submit an NCAR or not. This makes the interpretation of the limited data available via the NCAR summaries difficult.

10.3.2. Data submitted in National Competent Authority Reports

Box 10.5 contains the elements of data that the ANNEX of Decision 2020/227/EU requires be entered into Eudamed on incidents for NCARs.[449, the Annex]

NCARs are communicated in English through the NCAR Form provided in MEDDEV 2-12-1 revision 8.[445, Annex 8] This is a standardised form which, when completed, should contain the following information:

[i] This means that manufacturers can prevent their device from becoming the subject of an NCAR by acting in a timely manner.

- details as to the purpose of the information exchange (i.e. which of the exchange criteria triggered the NCAR);
- whether it is deemed to be as 'confidential' or 'non-confidential';
- the contact details of the reporting NCA;
- identifying details for the device or the device category which is the subject of the NCAR (name, ID number, medical speciality), and if it is a single device – the contact details of the relevant economic operators (manufacturer or his legal representative);
- background information to the report and the reason for the report (a description of what has happened, including consequences for the patients/users);
- an indication of whether an investigation has been initiated, is ongoing or complete, and any results;
- recommendations for the receiving NCA;
- a list of recipients of the NCAR.

(a) Competent Authority reference;
(b) Manufacturer, where applicable authorised representative (see fields under 1. Actor);
(c) Manufacturer contact;
(d) Manufacturer reference/Field Safety Corrective Action (FSCA);
(e) Device (Internationally recognised nomenclature code and the Device Name/Make or, where not available, generic name.), plus where applicable lot number, serial number, software version;
(f) Notified Body (selected from system);
(g) Device known to be in the market in; names of countries
(h) Confidential;
(i) Complete investigation;
(j) Background Information (Description);
(k) Conclusion;
(l) Recommendation;
(m) Action and action description.

Box 10.8. Data elements to be entered in Eudamed for NCARs

Thus information is communicated in a standardised format, improving the speed and effectiveness of the reporting process. This information is submitted to the Commission and the other NCAs via the EUDAMED system. If it meets the criteria for sharing through the IMDRF NCAR Exchange Program, it is also submitted by secure email[i] to the NCAR Secretariat for onward distribution to the relevant NCA(s). The form may also be sent to the manufacturer for consultation and comments, or amendments of the technical

[i] Submissions to the IMDRF NCAR Secretariat is done using the IMDRF NCAR form, which is slightly different to the EU NCAR form.

details, prior to submission to EUDAMED or the NCAR Secretariat. The form is used by the responding NCA(s) to answer questions that have been asked by the submitting NCA, as well as providing them with the information needed to investigate the issue.
Each NCAR exchange form issued is the subject of a single NCAR, with additional requests for information and responses being submitted as amendments to the original NCAR exchange form.

10.3.2.1. Analysis of NCAR data

The analysis cannot be in-depth due to the unreliable nature of the data and its sparsity of information, but it can be used to illustrate potential trends in AMDE rates over time. To do this, the data are presented in graphs to show the number of NCARs reported (in total and by the individual MSs). To illustrate differences, data were also segmented into three time periods: 2007-2011; 2012-2016; and 2017-2019. Between 2007 and 2011 it was not mandatory to enter data in Eudamed. The second period, 2012-2016, represents the transition period as it was mandatory to enter data into Eudamed in compliance with the requirements of the MDD. The third, 2017-2019, represents the period since the MDR was introduced in 2017. It is worth noting that the data is presented as annual data but the transitions took place in May of 2011 and 2017 respectively.
Data from 2020 are also included, but as the Covid-19 pandemic had huge impacts on healthcare delivery, including the cancellation or postponement of many routine or elective procedures, this is not representative of the normal situation. Consequently, 2020 data[i] aren't included in the three trend segments[ii].

10.3.3. Findings from the analysis of the NCARs

The findings are presented in Figures 10.4-10.6. Figure 10.4 shows the total number of NCARs shared in Europe between 2007 and 2019, whilst Figure 12.2 shows the data up to 2020. The figures demonstrate a steady rise since reporting began, with an almost fivefold increase in the number of NCARs over the period between 2007 and 2013. Since then the number of NCARs appear to have levelled off, with an average of approximately 982 NCARs being shared annually between 2013 and 2019.

[i] Due to the Covid-19 pandemic, the numbers of NCARs from 2020 have been omitted from the other figures as there are several reasons why they would not be representative of the normal situation; for example, NBs were unable to perform audits and approve CE marking for new devices and many planned elective operations did not occur, reducing the number of people who could suffer an AMDE.
[ii] It has not been possible to locate the NCAR summary reports for 2021-2023.

Figure 10.4: National Competent Authority Reports 2007-2019

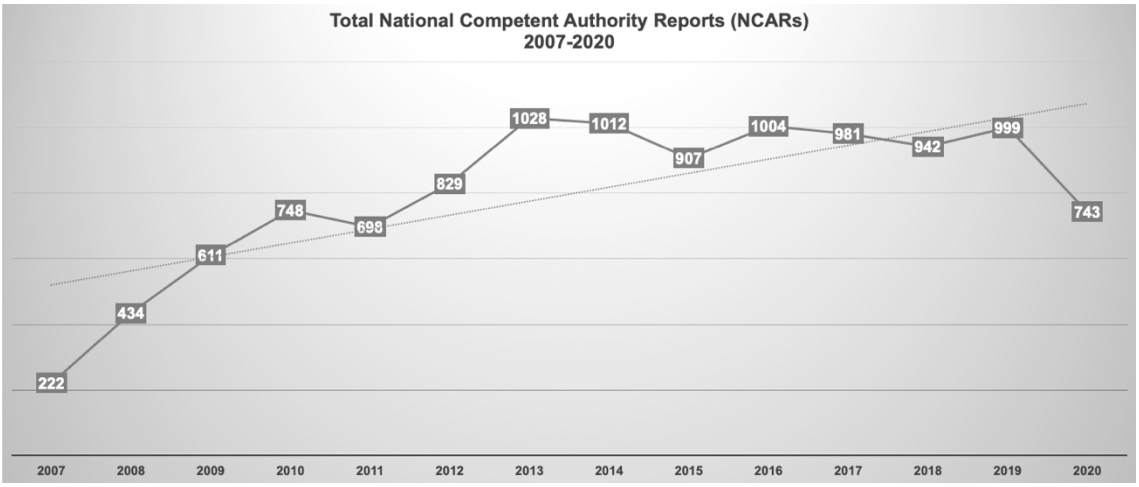


Figure 10.5: NCARs 2007-2020

However, not all countries are reporting, as is illustrated by Figures 10.6-10.7. Ninety-eight percent of reports shared between 2012 and 2019 were shared by ten countries, whilst the top six reporting countries shared ninety percent of the total reports. On average, across the reporting period (2007-2020), there were seventeen countries submitting NCARs, the fewest being in 2008 with only fourteen countries sharing and the highest being nineteen countries reporting in 2010 and 2020.

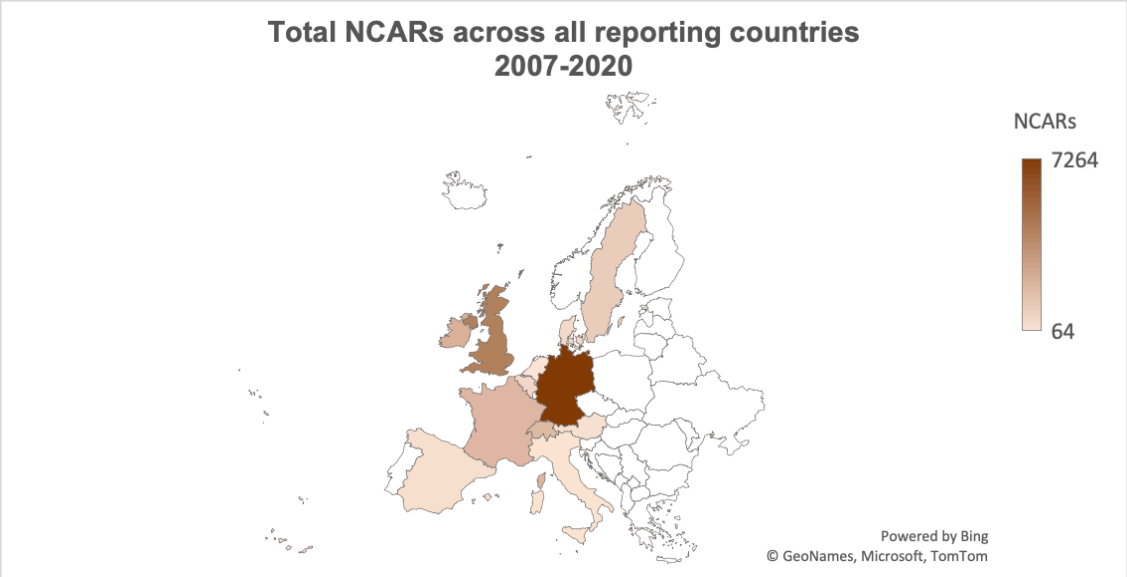


Figure 10.6: Map illustrating geographical distribution and density of NCARs 2007-2020

Figures 10.7-10.8 clearly show that Germany and the UK are the top two reporters of NCARs.

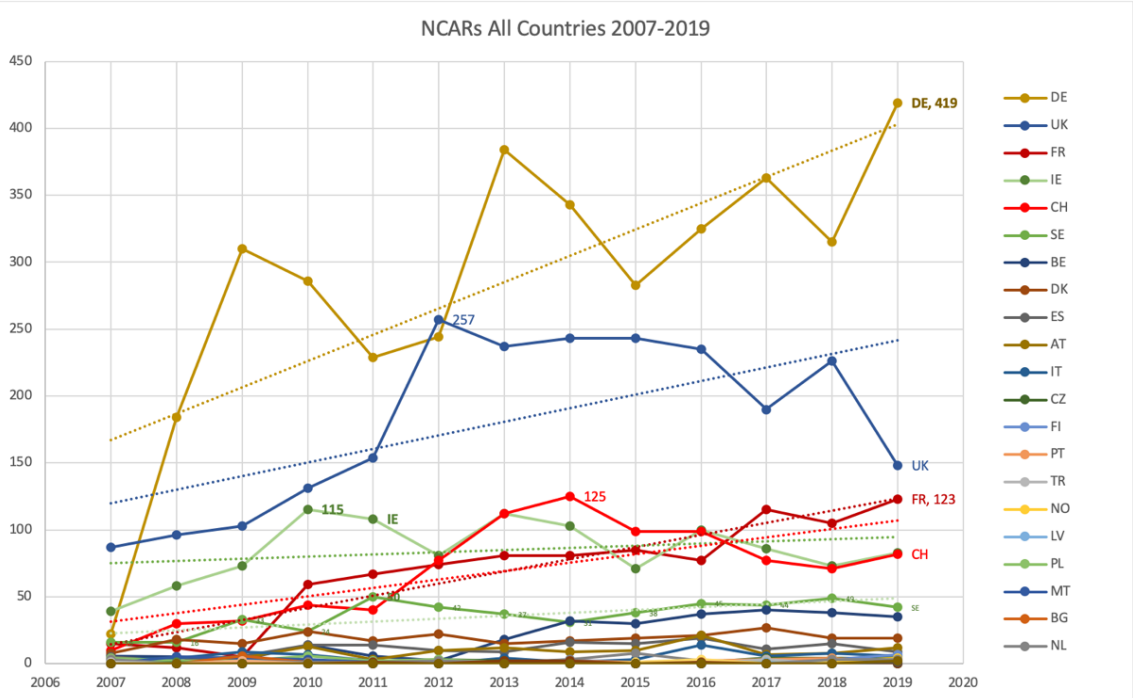


Figure 10.7: Annual reporting of NCARS by country

Figures 10.7-10.8 show that Ireland is one of the top six reporters of NCARs. Ireland was consistently the third highest reporter between 2007 and 2012 and has varied between the fourth and fifth highest since then. Since 2012, Ireland been overtaken by France whilst Switzerland is now on a par with Ireland, sharing about the same number of NCARs as Ireland on average. However, with the UK no longer submitting reports in

2020, and with a drop in the numbers being reported by all countries, Ireland was the second highest reporter in 2020.

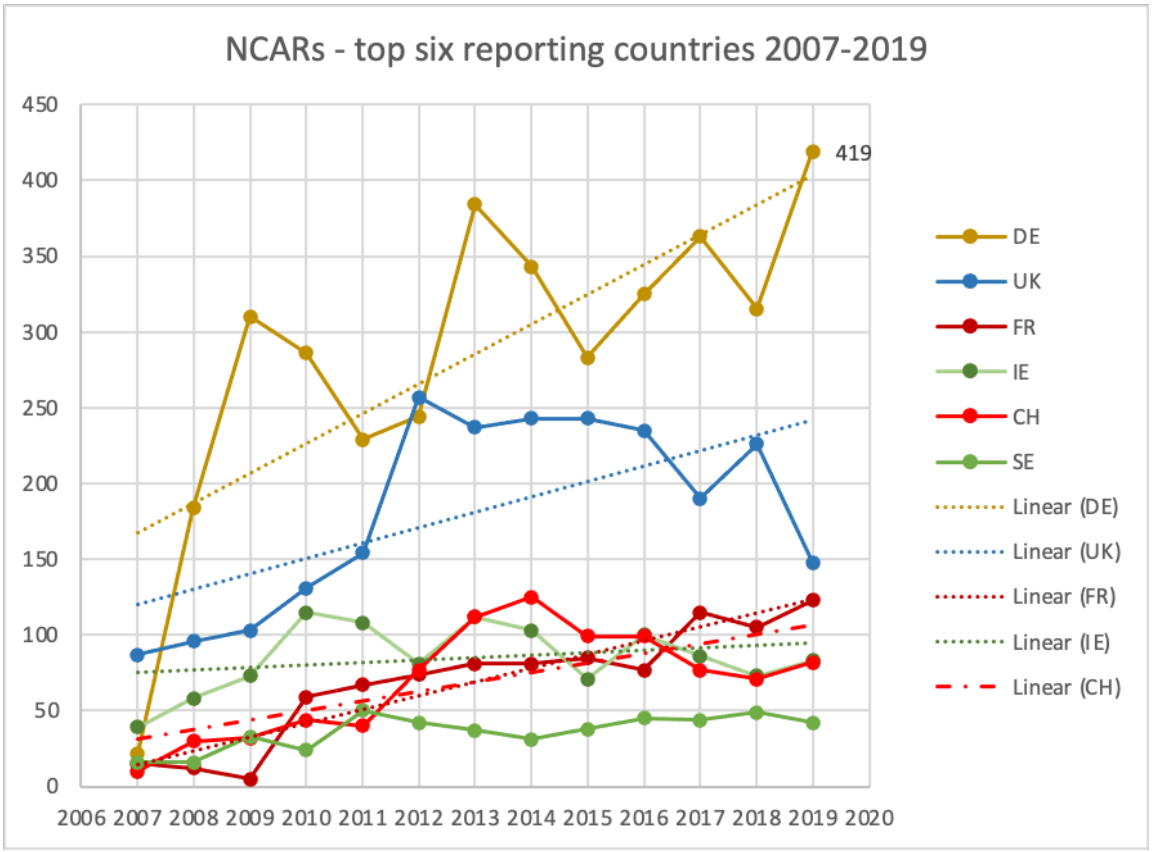


Figure 10.8: NCARS reported by the top six reporting countries 2007-2019

There are a number of possible explanations for the reporting trends presented in these figures, ranging from factors related to the devices themselves to system-related or/and country-specific factors. However, even at the beginning of reporting there was a difference between countries in the numbers of NCARs shared. Figure 10.9 shows the number of NCARs being reported by those countries that do report but at lower levels than the top six reporters. It also suggests an upwards trend between 2007 and 2013 for most countries, apart from Belgium, but a levelling off between 2013 and 2019 at a higher rate, with perhaps a slightly upward sloping incline.

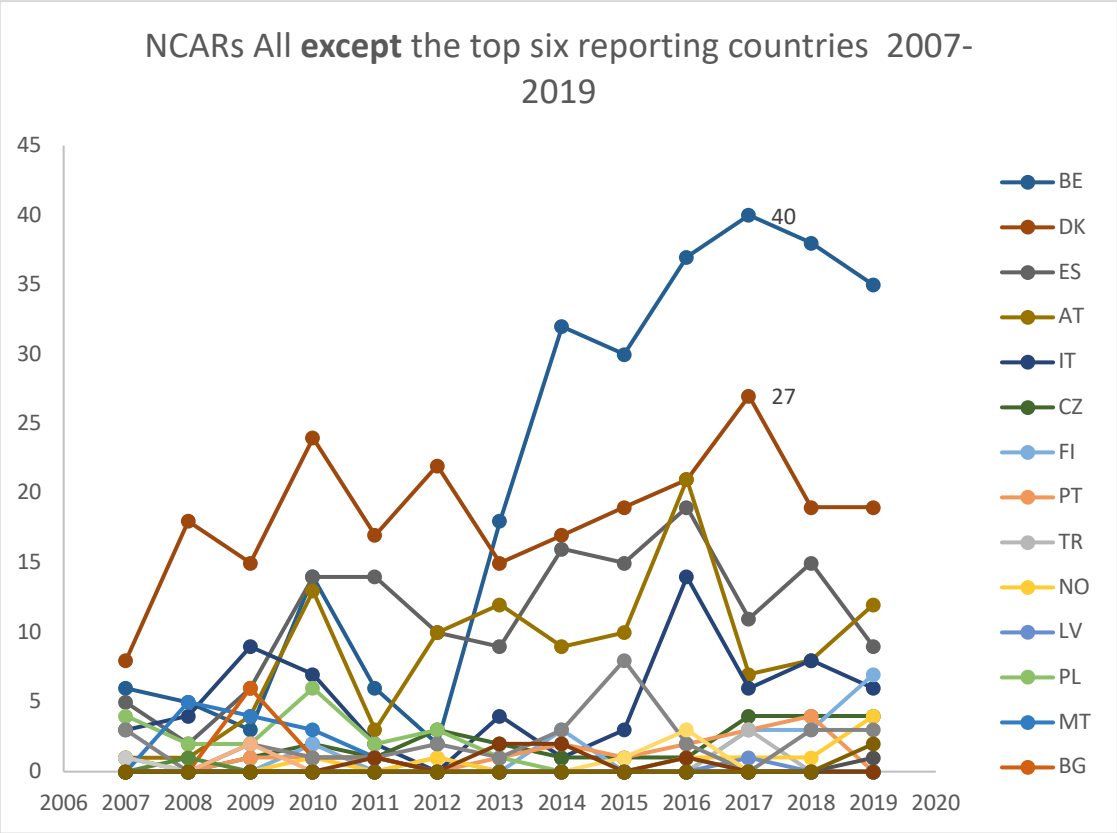


Figure 10.9: NCARS reported by all countries except the top six reporters 2007-2019

The trendlines highlight that the numbers of NCARs reported by Ireland hasn't changed significantly over the last eleven years, whereas the numbers originating from Germany, the UK, France, and Switzerland have clearly been increasing, with a significantly greater rate of increase in NCARs coming from Germany and the UK as compared with a relatively slower rate of increase of NCARs reported by France and Switzerland (Figures 10.7-10.8).

However, if we assume that it took some years for reporting to become established practice, and if we assume that it had reached its steady state by 2011 (as it was known that it would be mandatory by then), and look only at the rates of reporting from 2011 to 2019, we see a slightly different picture. Taking Ireland and Germany as examples, we see in Figures 10.10-10.13 that there is a more steady rate of reporting, and although the reporting rate for Germany is increasing, it is at a much reduced rate of increase.

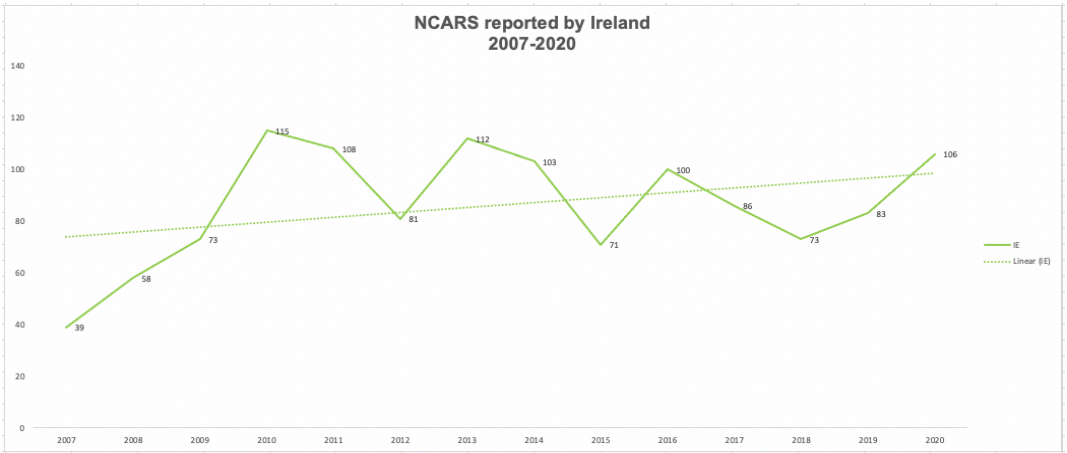


Figure 10.10: NCARs reported by Ireland 2007-2020

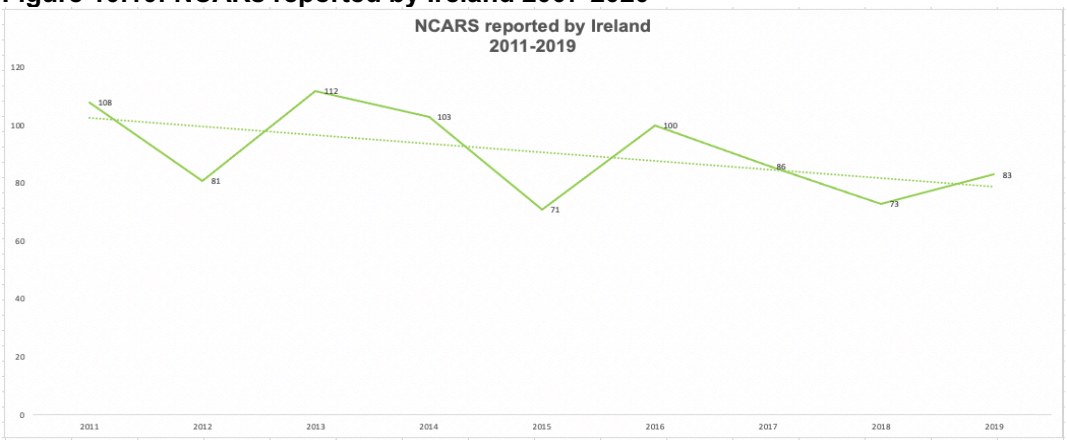


Figure 10.11: NCARs reported by Ireland 2011-2019

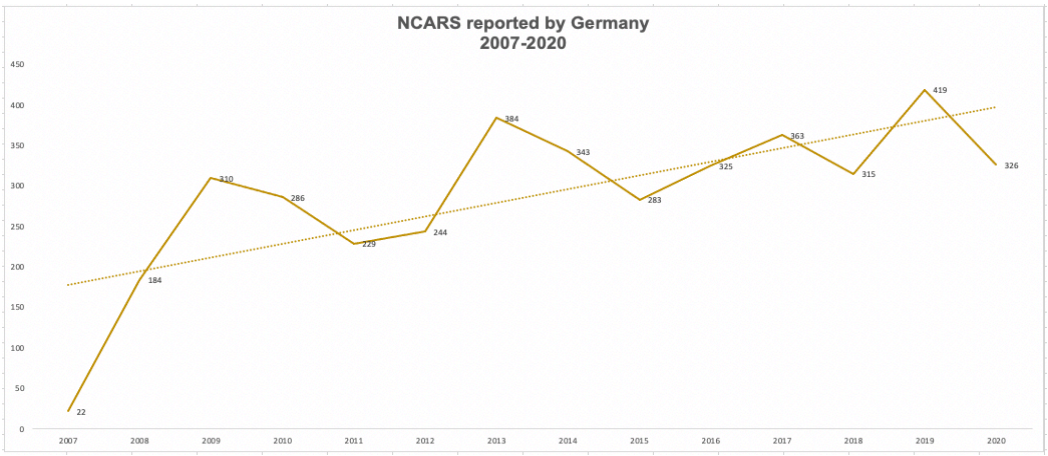


Figure 10.12: NCARs reported by Germany 2007-2020

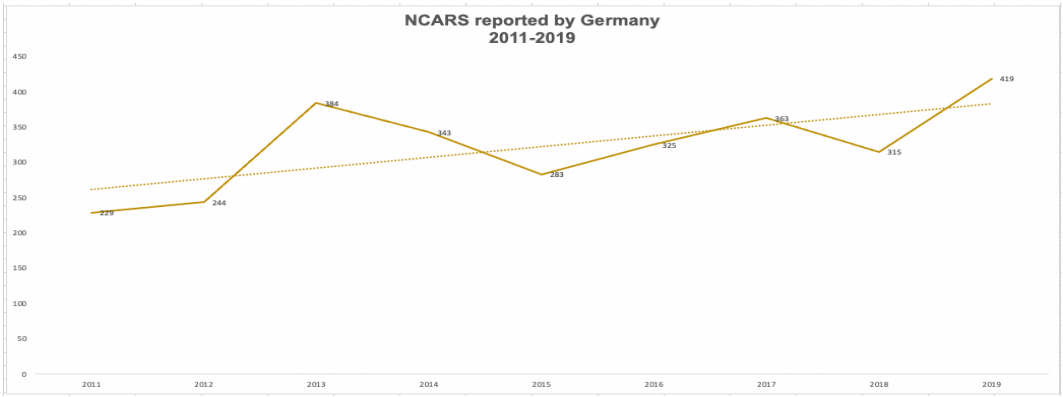


Figure 10.13: NCARs reported by Germany 2011-2019

With access to Eudamed in 2004, some NCAs may have already started to input data, and certainly by the time NCARs were being shared in 2007, there were 222 NCARs shared by sixteen MS. The numbers of NCAs participating in the NCAR scheme haven't varied greatly over the entire period, although several countries report only one or two, and sometimes no cases, each year. Between 2007 and 2010 there is a clear trend in increased numbers of NCARs, with a few countries separating out from the rest as their numbers increase disproportionately to the other MS. Between 2011 and 2016 this tends to level off, though at a higher level than previously. This trend in levelling off is also seen between 2017 and 2019, when Germany is the only MS with NCAR numbers still increasing. The NCARs from France and Switzerland have also increased between 2017 and 2019, but not much beyond the average level around which the other countries are clustered.

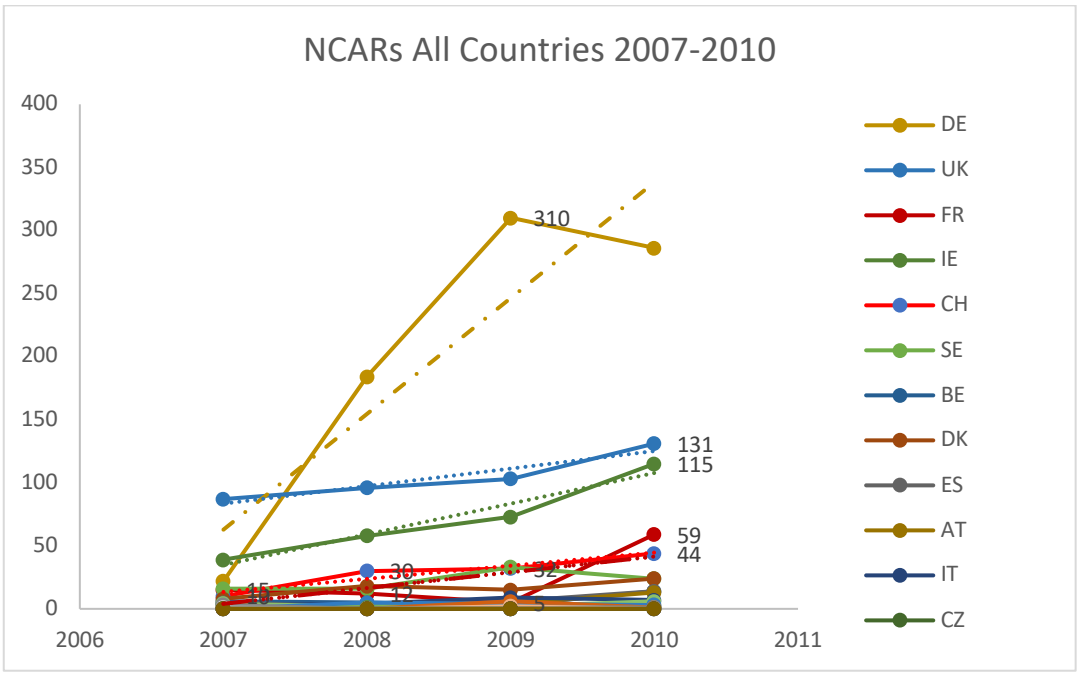


Figure 10.14: NCARS 2007-2010 - prior to mandatory reporting to Eudamed

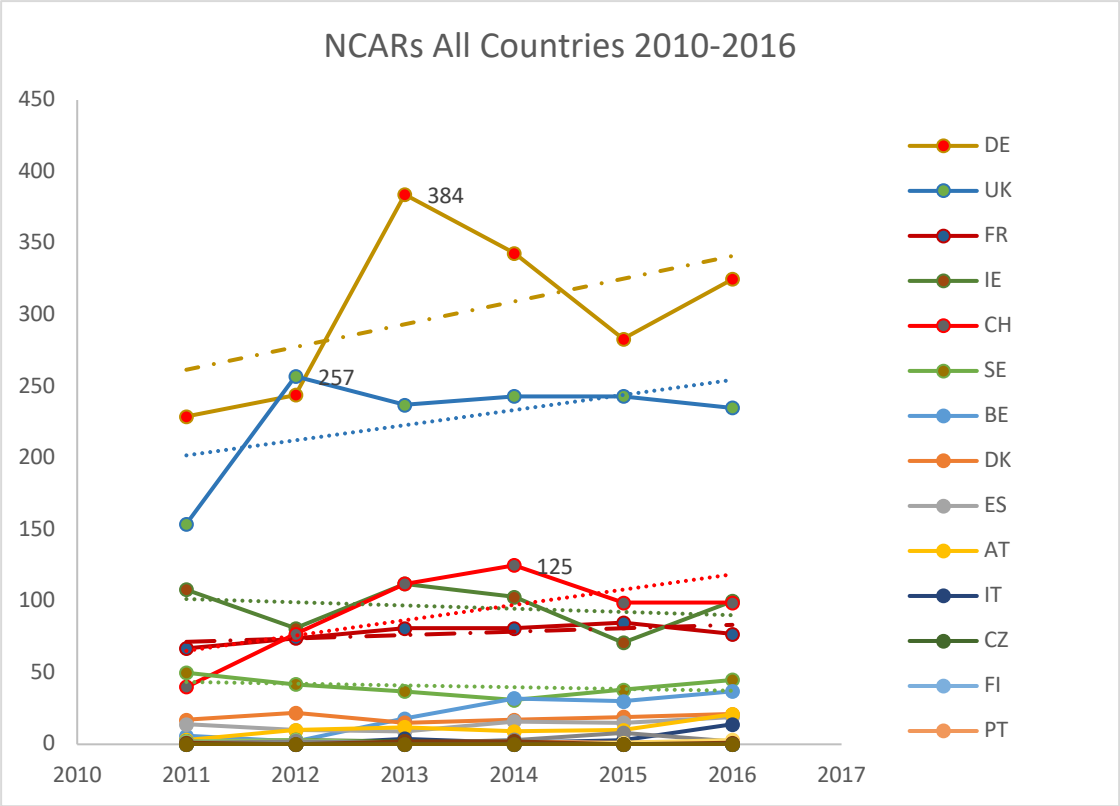


Figure 10.15: NCARs 2011-2016 - with mandatory reporting but prior to the MDR

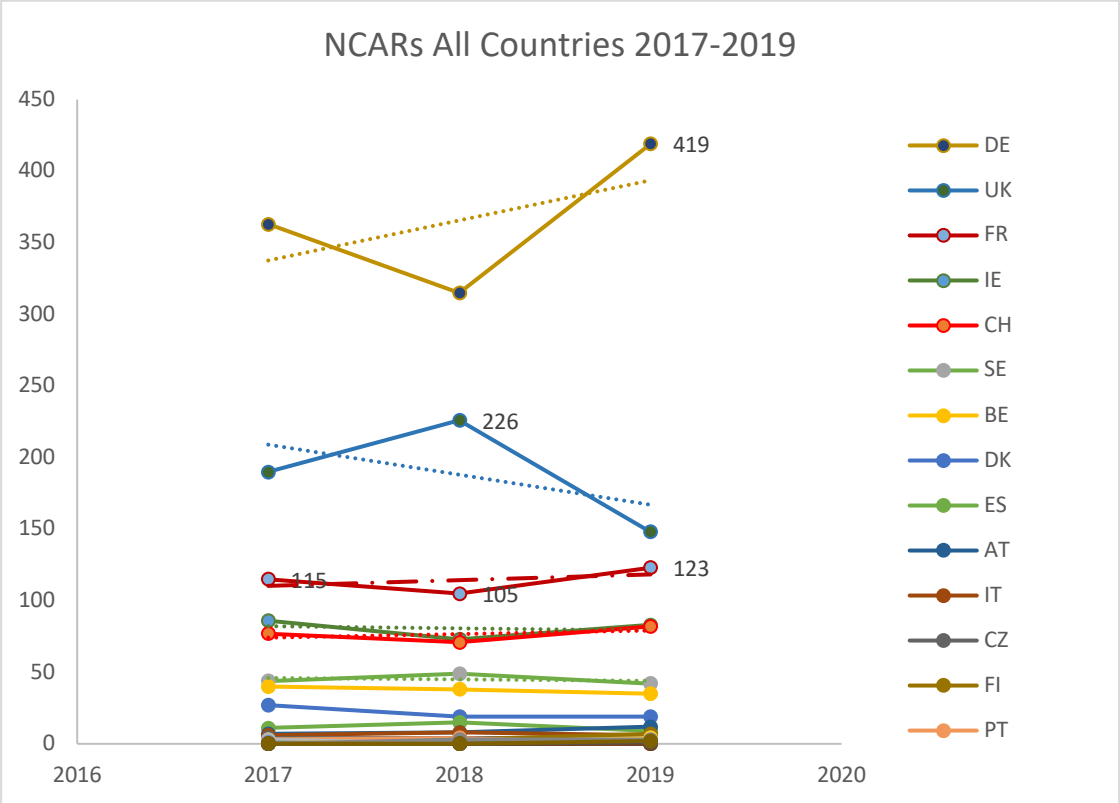


Figure 10.16: NCARs 2017-2019 – with mandatory reporting and MDR introduced

In conclusion, the numbers of NCARs have increased at least fourfold since the Eudamed first started collating the statistics in 2007. However, this increase appears to be due, at least initially, to the establishment and routinisation of the practice of reporting. Since becoming a more established practice, the numbers have tended to increase slowly, but it is unclear whether this later increase is a reflection of better detection, better reporting, poorer medical devices, or other factors; or if it is significant at all.

Furthermore, it is not possible to infer whether the regulation (or changing it) has had any impact beyond the initial period where the legislation mandated reporting. We can conclude that reporting is now a well-established practice in some, but not all, countries. However, this is not the same as impacting safety, about which we can make no inferences, except to say that approximately 1000 devices (i.e. device types, groups or categories) a year are causing serious AMDEs in the EU. How many patients these 1000 devices are affecting remains unknown.

10.4. Discussion

10.4.1. Implementation

There are several targets within the MDD. It might be argued that the primary targets are the manufacturers and other economic operators involved in designing, manufacturing, sterilising, packaging, labelling, or selling medical devices, and that the MDD is aimed at changing their behaviour to ensure that their devices meet the essential requirements of the MDD, with the aim of ensuring their safety. However, it is equally plausible to suggest that the MS are in fact the primary target, whose behaviour must be modified so that they don't prohibit the placing-on-the-market of medical devices that comply with the requirements of the MDD. In fact, I would argue that the MS are the primary targets, because previously they had different safety rules that posed a barrier to the free movement of medical devices, and it was for this reason the New Approach was introduced. Furthermore, the MDD states that is addressed to the MS, which means that they are legally responsible for compliance.

The main processes that the MDD attempts to regulate are the design, manufacturing, sterilising, packaging, labelling, placing-on-the-market, surveillance and clinical investigation processes, which it does mainly through the CE marking process and the requirements imposed by that. However, the complexity of the regulatory system hides the fact that there is a lack of data publicly available to evaluate medical device safety and efficacy. While we often assume that data on clinical efficacy does exist – but is too difficult to find – we rely on the regulator's judgement of the evidence to ensure that only safe and effective devices are allowed onto the European market.

Yet, as this section on implementation shows, it is the manufacturers who assess the conformity of their medical device(s) with the essential requirements (ER/GSPR). They have the data; they decide whether it is sufficient to demonstrate compliance with the ER/GSPR or whether a clinical investigation is needed (and if so, whether to publish the results in the literature); they decide which notified body to use to verify their conformity and which CAP to follow; they decide the intended purpose, the indications for use; they identify the potential benefits and risks and decide whether the benefit-risk balance is acceptable or not, and which standards to use; they decide how to manage the risks and what information to supply with their device. If it were a medicine the manufacturer wouldn't have all those choices, and specifically, the regulator would be responsible for determining the indication for use. This evidence gap is largely as a result of the lack of a regulatory requirement to produce and present it and a lack of policy response to the need for better evidence for healthcare interventions.

The MDR doesn't fundamentally change the regulatory approach of the MDD, it relies on QMS and risk management to improve quality and reduce the risk of product failure, and PMS to detect failing devices once on the market, but it still doesn't mandate evidence of effectiveness prior to market entry, relying on conformity assessment to assure legal compliance rather than adopting a centralised system of market authorisation based on critically appraised evidence of efficacy. Although it does introduce changes that may improve safety, and should improve transparency of the evidence, however, that remains to be seen.

10.4.2. Safety outcomes - Discussion on NCARs

There are a number of things to point out about the NCARs. Firstly the data was difficult to find; indeed, its location on the official EU website changed during the course of the research. This reflected the shift in responsibility for the oversight of medical devices – and hence for Eudamed and the NCAR summary statistics –from DG GROW to DJ Santé with the change of Commission in 2019.

Not only was the data difficult to find it was also difficult to interpret, because the meaning of some of it was unclear. For example, the denominator was not described for the reported percentages presented in any of the NCAR reports. Moreover, despite being very short, the NCARs contain mistakes. For instance, the EU country codes cannot all be correct because they include SL (Sierra Leone) and FL (which is likely meant to be FI – Finland). In addition, whilst there are very clear reporting criteria described by the GHTF and the IMDRF, the EU reporting criteria remains less clear.

Thus even when the data is available, it is generally not easily accessible nor interpretable. This demonstrates yet again the lack of transparency regarding medical

device safety. This evidence cannot support the theory that it is serving the public interest. However, it does support the theory of private interest regulation as it prevents any alarm or loss of public confidence in the safety of medical devices or in the CE marking process.

Secondly, from the little data that is available, it is clear that the risk class of a device is not a guarantee that the lower risk classes pose little or no threat to people's health. It is true that the proportion of AMDEs attributable to the lower risk classes is significantly lower, because of the much larger number of these devices, but nevertheless, the data suggests that they can still be the cause of serious or life-threatening AMDEs. Indeed, US data demonstrates that 'lowest-risk' devices, equivalent to EU Class I devices, are still subject to the most urgent level of recall (Class I recalls), activated when the FDA has received reports of serious or life-threatening AMDEs. In fact, data from the 2007-2011 NCAR summary report, would suggest that Class I devices are the subject of approximately 15% of NCARs, indicating that they posed serious risks to patients.[468]

Thirdly, the rate of serious AMDEs appears to be increasing over the reporting period (since 2007). The occurrence of the PIP scandal in 2010 and the metal-on-metal hip failures in 2012 may have contributed indirectly to the increased numbers of NCARs being reported by making people more aware of the possibility that medical devices might not be as safe as expected.[i]

Fourthly, reporting varies across countries, which may be due to a variety of reasons, but since the data is so poor it is not possible to investigate any of these possibilities. A review of the GHTF NCARs Exchange Program, presented in 2012, concluded that there was also an unequal participation in the GHTF NCAR Exchange Program.[469] The difference between Germany and the other NCAs may be due to its very large medical device industry. However, if that were the main reason it would be expected that the numbers of NCARs should also be high for Italy, and that Ireland's number would be smaller than Germany's but increasing at a similar rate. It could also be attributed to differences in population size, in which case Italy, Spain, and Turkey would be expected to be contributing significantly more NCARs than they are. It may also be that the detection of NCARs is better in the top six reporting countries than in the countries sharing few or no reports. If this is the case, then the true rate of serious AMDEs is far below the number of NCARs shared.

Finally, according to the guideline, MEDDEV 2.12-1 Rev 8 on vigilance, "The principal purpose of the Medical Device Vigilance System is to improve the protection of health

[i] However, they could only directly contribute a single NCAR each to the total number, because each NCAR relates to a single device or device category. There may be several rounds of communication on each NCAR, but this doesn't add to the number of NCARs exchanged.

and safety of patients, USERS and others by reducing the likelihood of reoccurrence of the INCIDENT elsewhere"[capitalisation[i] in the original][445, p.4] However, this means that an incident must occur to someone first, so it is not primary prevention but rather secondary prevention of AMDEs.

10.4.3. Themes in the data

Thematically linking the findings of this section with the findings in previous sections, it becomes clear that there is a lack of data and a lack of transparency due to the confidentiality requirements. These confidentially requirements stem not only from the legislation but also from the GHTF/IMDRF guidelines, and the confidentiality requirements for sharing NCARs. All of this points to a private interest theory of regulation rather than a public interest theory, because it is in the public's interest to hear about AMDEs contained in the NCARs as soon as possible, yet these cannot be made public until after the manufacturer has made it public by submitting a FSCA to their NCA.[445, p.31]

[i] Capitalisation in the MEDDEVs and in Standards documents indicates that the term that is capitalised has a specific meaning, which is defined in the definitions section of that document, which in this case is Section 4 of MEDDEV 2.12-1 rev8.

11. Discussion

This chapter attempts to tie together the many threads of this research. It starts with a summary of the findings (Section 11.1), followed by a description of cross-cutting themes (Section 11.2). Section 11.3 returns to the conceptual framework guiding the entire project, reflecting on how the research findings fit together to propose a potential explanation. Section 11.4 describes some reflections on my role as a researcher and how I interacted with the data. Section 11.5 addresses the limitations and strengths of the research. 11.6 discusses the implications for policy, practice, and patients.

11.1. Summary of Findings

The lifecycle review showed that the lifecycle approach to evaluation is being adopted or promoted by HTA bodies and clinicians in order to address the gap in the clinical evidence. However, the medical device lifecycle and lifecycle evaluation don't mean the same thing to everyone with different people are looking for different evidence to address different decisions. Consequently, lifecycle evaluations produce different results. Furthermore, it was the adoption of the lifecycle approach to regulating medical devices, allowing evidence generation to be deferred until the post-market phase, that resulted in the lack of adequate evidence for clinical and reimbursement decision-making.

The regulation review showed the complexity and fragmentation of the regulatory process and the dynamic nature of legislation that makes it difficult for ordinary citizens to understand it. These factors conceal the fact that the EU regulatory framework for medical devices is primarily designed to remove barriers to trade, and that safety (due to the differing safety requirements imposed on products by the MS) was the cause and not the goal for the original legislation. Consequently, it was not designed to benefit patients nor to ensure the safety and efficacy of devices being placed on the market, it was designed to remove barriers to trade. It utilises a quality management system to limit the risk of device failure due to poor design or manufacturing processes. Yet good quality does not mean that a device is clinically effective. Devices are not approved, instead manufacturers are allowed to affix the CE marking, which is essentially a quality mark, following successful completion of an approved conformity assessment procedure and verification by an organisation contracted by the manufacturer to assess their legal compliance with the requirements. Manufacturers are not required to provide robust evidence that their device is clinically effective. Once on the market it is assumed that a device is effective. Bolstering this assumption, post-market data collection concentrates on sources of evidence for adverse events to assess a device's 'continuing' safety. However, reporting of AMDEs is notoriously poor for a variety of reasons,[87] which means that the lack of incident reports continues to reassure clinicians and the public regarding

the safety of devices. Realising the need for better data, several professional or clinical societies have established implant or patient registries. However, many of the implant registries also concentrate their efforts primarily on detecting failing devices rather than assessing their clinical effectiveness or effects on quality of life or overall survival.

11.2. Cross-cutting themes

11.2.1. A multi-level problem

A cross cutting theme across the research was the multiple levels at which a concept could be applied. There are multiple levels of regulation, multiple levels of conceptualising a medical device, and multiple levels of decision-making, which Rogers refers to as '*decision-making units*'.[123, p.171]. Figure 13.1 shows the multiple levels of decision-making units that exist.

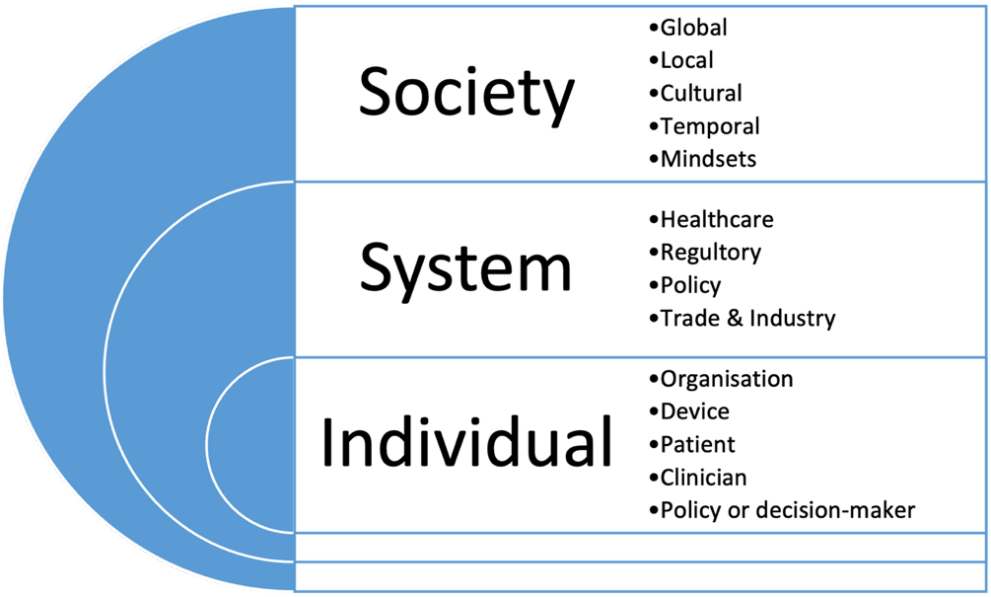


Figure 11.1. Multiple levels of consideration

Each of these influences the others in a similar way to the interactions described in Bronfenbrenner's Ecological Hierarchy that influences the development and health of a child.[470–472] This means that isolating one set of ecosystems to identify the causal and contributory factors to a problem, such as medical device safety, necessarily takes it out of context and, as Greenhalgh et al. explain, this fails '*to address important interactions between different levels (for example, how different organisational settings moderate individual behaviour and decision making)*'[294, p.334] They suggest that conducting '*meso*' level research, exploring interactions between the micro and macro (i.e. the individual and organisational) levels, could further understanding on the effects that different organisational structures and cultures have on decision-making by particular groups of individuals.[294, p.334] In this research it became clear that those generally considered to be

the regulators, the CAs, have little power to control unsafe or ineffective devices in the market. Furthermore, they frequently lack the necessary knowledge to make a decision to withdraw or restrict a device. They may appear to be the regulators, but their ability to control is impacted by the regulatory policies that they must operate under, which are determined, in theory, by the EU's regulatory institutions. However, even these institutions are subject to various influences. The regulatory approach espoused by WHO and GHTF have clearly influenced or been influenced by the approach adopted by the EEC, and that didn't change much with the EU's adoption of the NLF guiding the contents of the MDR. Industry has been involved in developing GHTF guidelines, which the WHO model regulatory framework is largely based on. At the EU level, industry has also influenced the direction of EU legislation. Indeed, the rapporteur tasked with driving the revision process on behalf of the EP, expressed anger at the level of lobbying by industry to influence the process.[41]

11.2.1. Regulatory Capture

The EU regulatory framework for medical devices is avowedly intended to serve the twin goals of maintaining (or improving) public health and removing technical barriers to trade across the EU. Indeed, with the MDR, the legislators at least tried to improve post-market safety processes. However, this analysis shows that within EU legislation the power given to achieve the public health goal is very little, whilst the power given to achieve the trade goal is much greater. Notified bodies were considered to be, in effect, servants of industry rather than objective assessors of manufacturers' compliance with the legal requirements.[393, p.71] This documentary analysis of medical device regulation, thus, demonstrates evidence of regulatory capture.[473]

In fact, 'capture' can occur across multiple levels to influence our thinking, norms, attitudes, knowledge, understanding, and the evidence requirements (or even what is considered to be evidence), or what 'evidence' is acceptable, for decision-making.[474] This was demonstrated by the lifecycle review where there was near universal acceptance of the belief that innovation is important, and the attitude of unallayed hope that new products will be better than older ones, which in turn lowers our demands for evidence and fosters acceptance of limited evidence for reimbursement and clinical decision-making. The MDR demands evidence to support claims regarding performance and the benefit-risk determination rather than clinical efficacy, accepting evidence of these from predicate devices or from observational data.[85] Additionally, it continues to rely on HS as a means of proving and assessing compliance, yet industry is intimately involved in drafting these standards. Furthermore, the GSPR in Annex I of the MDR states that medical devices '*shall be safe and effective'*, yet this is not reflected in MDCG

guidance. The fact that this requirement is stated in law, yet apparently not required in practice is an important policy issue – why is it being ignored? This certainly doesn't serve public interests.

The findings from this research resonate with the emerging body of literature exploring commercial determinants of health, which reveals industry strategies to influence policy or regulatory decisions affecting their products' marketability, including ways of influencing public perception to allay (justified) fears that products may be harmful.[475–482]

11.2.2. Different goals, different motivations

Different Actors have different goals and motivations for fulfilling their own tasks and for influencing others to adopt particular approaches to theirs. This was seen in the review of lifecycle evaluation models and even within the regulatory framework for medical devices. Industry stakeholders use lifecycle models to find ways to increase sales, market share, or profits. This must be remembered in the context of industry rhetoric encouraging lifecycle approaches to evaluation. Lifecycle evaluation means that the device is being sold while other stakeholders are still trying to determine its safety and efficacy. Industry has a major influence on the adoption of devices, regardless of the evidence underpinning them. For example, Wilson explains that '*The primary driver of spinal instrumentation is the industry that manufactures spinal devices, which runs workshops to teach surgeons how to use its products*.'[483] As long as patient safety and clinical efficacy outcomes remain unclear,[i] manufacturers can continue to sell their device. Moreover, the assessment process remains bound by confidentiality, obscuring the fact that the competing goals of supporting innovation/trade and maintaining public health are almost all balanced in favour of the former.

11.2.3. Framing of device safety

Framing EU medical device legislation first and foremost as a solution to ensure the safety of a product, rather than as a means to enhance trade, serves to engender confidence in the regulated products.[484] Yet, this was not the primary purpose underpinning the legislation, and it creates a false sense of security, thereby lulling purchasers, and even those tasked with rule enforcement, into complacency regarding vigilance and surveillance.

Furthermore, industry often supports patient organisations to lobby for greater and earlier access to innovative technologies. This further frames the conversation in terms of patient access instead of market access. Framing the policy issue as one of patient access to innovative devices shifts the focus from the need to generate better evidence.

[i] or indeed if they demonstrate true superiority to other alternatives

Rather than provoking calls to strengthen the evidence base, this leads to free market thinking that developing better ways of using less evidence is necessary to ensure rapid access to innovation, even if the innovation is not yet proven to be beneficial. Greenhalgh describes a pro-innovation bias that is evident in the acceptance of the need for rapid access to new technologies, despite the evidence that innovations that enter the market more quickly with less rigorous pre-market regulatory appraisal are more likely to cause harm, and are less likely to be beneficial, than those that go through more rigorous, albeit slower, appraisal processes.[59,485] In fact, the push for more rapid access, with less evidence and less rigorous regulatory review, further exacerbates the lack of data available to assess the efficacy and effectiveness of a device,[309,322] and post-market studies required by regulators generally do not address this shortfall in the evidence.[29,316]

11.2.4. Communication

Communication influences our knowledge, understanding, and attitudes to ideas, concepts, innovations, people, places, processes, and virtually everything.

Just as there exists the possibility of regulatory capture, there is also the possibility of 'knowledge capture', 'understanding capture', and 'attitude capture'. 'Knowledge capture' entails controlling what knowledge is made available, such as keeping important information confidential. 'Understanding capture' entails changing how people attribute meaning to concepts, for example, what is understood by the medical device lifecycle, lifecycle evaluation, and 'real world evidence'. 'Attitude capture' entails changing people's minds, values, or influencing them to be pre-disposed towards or against a concept. For example, when people's attitudes are inclined to favour innovation and desire access to the newest products on the market rather than being wary of the risks of a device with an unproven track record. Knowledge capture, understanding capture, and attitude capture, can occur through strategic marketing, which enables manufacturers to influence consumer values and users' understandings' of product safety, including risks.[486]

The lifecycle review illustrated the use of lifecycle evaluation models as a means of communicating ideas that influence what we do and don't know, perceive, understand, or value. The regulation review demonstrated that what is communicated is subject to legislative constraints and demands (e.g. confidentiality clauses and mandated notification of relevant information to the Commission). It also illustrated how communication may be framed to focus attention on certain aspects, and not on others, to divert attention and convey particular messages. For example, in Annex I, the MDR states that devices 'shall be safe and effective', but also that they 'shall achieve the performances intended by their manufacturer'. By juxtaposing the two concepts the MDR

sends a subliminal message that they mean the same thing. Yet these two concepts are not the same thing. Performance relates to how well a device functions, which places the focus on the device, whereas effectiveness relates to how well the patient is doing, placing the focus on the patient. A device may perform as intended but still not produce the desired clinical effects. However, no further mention is made in the MDR regarding devices being required to be effective, all requirements imposed on manufacturers to meet the GSPR require demonstration that the device performs as intended and the benefit-risk balance is acceptable.

11.2.5. Evidence

The call for the generation and provision of reliable evidence on health technologies in a timely manner for healthcare providers and funders has been made for a long time, but despite repeated calls for appropriate, reliable and timely evidence this call has not been answered to date.[487] Indeed, several authors have looked at the evidence underpinning medical devices and demonstrated that it is poor,[30,75,86,302,303,305,307,488,489] or worse still, that the evidence suggests that unsafe and/or ineffective devices are being used.[35,490–492]

High-profile scandals, which contributed to a loss of public confidence in the safety of implantable devices, put pressure on the EU to revise the legal framework in 2017, to increase requirements that manufacturers provide clinical evidence. EUnetHTA has also attempted to improve the evidence base by taking a lifecycle approach involving EDs with manufacturers to improve their clinical study designs and PLEGs attempting to find ways of generating reliable evidence in the post-market period.[291] Yet, despite this, there is little sign of systemic improvement in the evidence base.[285,493]

Hulstaert et al. suggested that if manufacturers would generate the evidence needed for reimbursement decisions by healthcare payers earlier in the process of bringing the technology to market it would mean that reimbursement is possible as soon as the product is placed on the market.[31] However, to result in earlier reimbursement this presumes that earlier evidence, suitable for HTA, will demonstrate that the product is safe and as effective, or more so, than its competitors. Yet, if this were likely to be the case it is also likely that manufacturers would already have adopted this strategy. They invest heavily in understanding and improving both the time to market and the rate of diffusion of their product. They have to take into account the alternative possibility, if the product doesn't demonstrate sufficient efficacy or added therapeutic benefit, or not enough to justify the premium prices that are asked for new technologies, then it won't be reimbursed at all. This means that without evidence a manufacturer may be reimbursed to a certain, though perhaps lesser, extent than if they provide evidence that

demonstrates efficacy or added therapeutic benefit, but they will be reimbursed substantially more than if the evidence were to demonstrate that the technology is no more effective and/or safe than the current available alternative technologies or if it is found to be less effective or safe. This is supported by the findings of Kisser et al, who showed that reimbursement decision-making for the highest-risk devices did not depend on the evidence, with many being funded despite a lack of evidence.[494]

In addition, there is a constant push to bring a technology to market as early as possible because the majority of the costs are incurred during its design and development phase but there are no financial returns until after market launch. There is thus, a significant conflict of interest for manufacturers to generate or provide evidence that may be desired or required by public reimbursement authorities but that may not be needed to place their product on the market. Indeed, the literature suggests that the desired evidence may not be required to secure public funding.[494,495] Consequently, as long as they are not legally bound to provide the evidence in order to legally market their devices there is little hope of the evidence-base improving.

The MDR has tried to address this gap by expanding the requirements for evidence that can be considered when assessing the conformity of a device to the essential requirements contained in the GSPR. This includes consulting databases of clinical evidence. Yet, apart from a few specific examples, these databases do not currently exist to any great extent, either in Ireland or more widely within in the EU. Thus the CE marking lends a degree of credibility that implies that, in theory, the evidence has been examined during the conformity assessment procedure, yet the lack of collated clinical evidence regarding the effectiveness and safety of implanted devices suggests this is not the case in reality.[75] Though it is hoped that this will improve for high-risk devices when the SSCP mandated under the MDR becomes publicly available, this remains to be seen.

It is therefore of crucial importance that clinicians and the public are aware of the shortcomings of the CE marking system. It does not guarantee either the safety or the efficacy of the technology. Furthermore, 'regulators' are prohibited (by the legislation governing the CE marking process) from making comparisons[i] between competing manufacturers or iterations of a device, though this is the evidence needed by clinicians and the public regarding whether a new technology is any better than an older one.[20,25,38,255,256,452,453,496–501]

[i] Although the MDR does to a certain extent now require manufacturers to make this comparison, or at least compile evidence on other similar devices to submit in their technical documentation.

11.3. Relating the findings to the conceptual framework

This section juxtaposes the findings from the research against the conceptual framework guiding it. Each of these could be applied to the multiple levels of decision-making units in Figure 11.1.

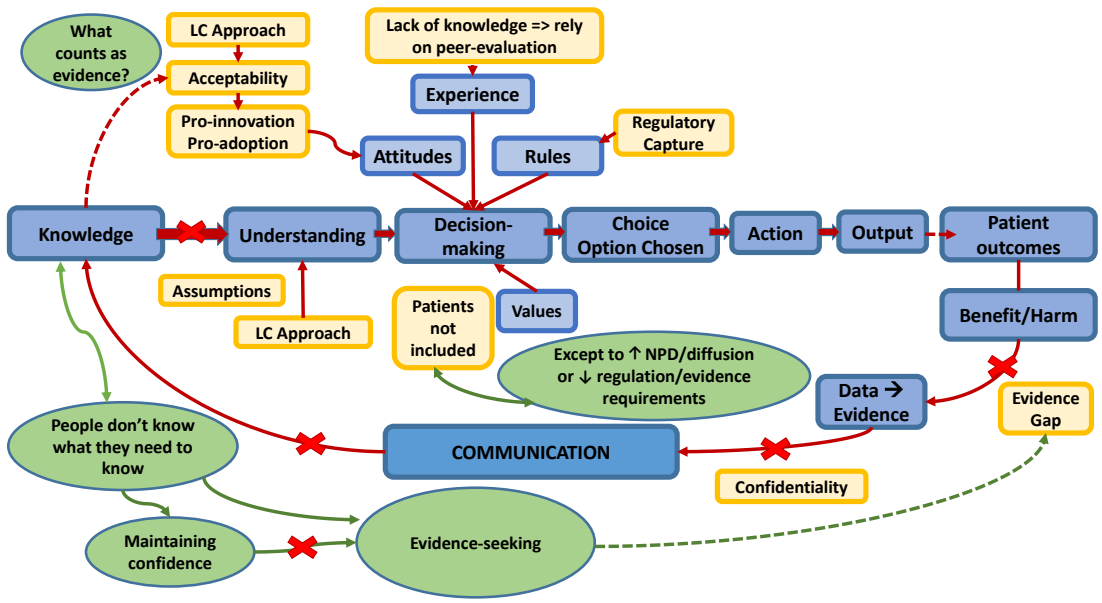


Figure 11.2. Relating the findings to the conceptual framework[i]

Knowledge

The knowledge required for clinical decision making in particular is not available, there is a gap in the clinical evidence required for understanding the safety and efficacy of any implant. Therefore, clinicians have to base decisions on imperfect knowledge. The reason the knowledge is not available is due to the confidentiality of the data underlying CE marking, even the clinical data, and the lack of knowledge or databases of clinical evidence for NBs to consult when approving devices.

Understanding and attitudes

With limited knowledge or evidence available to inform understanding of how safety is considered during the regulatory process (and the other processes, such as design and manufacturing), clinicians' and, consequently, patients' understanding is often based on assumptions and communications from industry and the regulators (encompassing the regulatory institutions of the EU, particularly the Commission; and international bodies that significantly influence the approaches adopted by regulatory authorities, such as

[i] **I would like to gratefully acknowledge that this graphic was created by Dr Monika Pilch from a drawing I made.**

WHO).[140 p.5] This in turn shapes clinician and patient attitudes towards the perceived safety of implantable devices.

Communication

Communication from the regulators and industry is often framed to suggest that the regulatory process is rigorous and is intended to protect patients. For example, MedTech Europe declares that '*Medical technologies are tightly regulated in the European Union*',[502] whilst the EU Commission announced the MDR as '*New EU rules to ensure safety of medical devices*'[503], citing stricter rules about using hazardous substances in implants, strengthening the rules '*generally*' for clinical evidence and clinical investigation, and highlighting the introduction of EUDAMED, patient implant cards, and individual device identifiers. However, it is clear that the communication from the Commission also sought to allay industry fears regarding the MDR, since they also highlight that the MDR will reduce their administrative burden, increase legal certainty, and improve the credibility and the '*reputation of the whole system*'.[503] This latter point is essential for ensuring consumer confidence and the acceptability of devices bearing the CE marking, a point that would not be missed by the major industry actors.

Communications from the Commission frequently convey the message that innovation is essential, promoting its benefits for healthcare and trade alike. Their landing webpage for medical devices presents an overview that states, '*Medical devices and In Vitro Diagnostic medical devices (IVDs) have a fundamental role in saving lives by providing innovative healthcare solutions…*'[504] implying that innovation is necessary for improving patient outcomes. This is a commonly held belief (which is not without evidence to support it) even in healthcare. For example, whilst being aware of the associated risks, Hannan et al. suggest that '*Innovation should be encouraged*' and that '*Forsaking new technology completely to avoid all possible risks to the public will reduce the quality of health care in the long run*.'[276, p.1, 4] However, uncontrolled diffusion of unproven devices causes significant harm, but much of this is undocumented (or dismissed as not important).

These messages reassure people that medical devices have been adequately assessed for their safety and efficacy, making it easier for key stakeholders to accept the lack of evidence on the assumption that this has been assessed and passed by the regulators.

Outputs

The outputs from each process differ. The design outputs include a design that is intended to meet the requirements captured. Manufacturing outputs are initially the prototype which is then tested for biocompatibility strength and durability; and eventually the product which is evaluated clinically from available clinical data. This clinical data

may include clinical investigations of the end-product, but it might not. The quality of the design and the manufacturing outputs are dependent on their quality systems and the risk management process.

Health technology assessment outputs are evidence syntheses produced to inform policymakers. However these depend on the data that is available, and since there is very little available, health technology assessments can only provide limited evidence.

Outputs from procurement are the products bought following a public procurement process, which are based on the requirements included in the request for tender. Procurement teams often have neither the skillset nor the time to assess the validity of manufacturers' claims regarding clinical efficacy, particularly with regards to long-term patient outcomes. Therefore, when choosing between competing tenders, procurement staff generally rely on quantifiable measures, such as price, to decide who wins the contract and which device(s) to purchase.

The outputs from use are the clinical processes and patient outcomes. However we can only know what these outcomes are if the data are gathered prospectively and systematically, measured objectively, and rigorously assessed. As this is not generally the case, patient outcomes are often not known, except by the individual treating clinician and/or the patients themselves.

Outcomes

These may be known or unknown, both in terms of their benefits and their harms. However for the most part they're unknown. Harms are often dismissed by clinicians as unfortunate, but not unexpected risks, that are the consequence of the treatment.[505] In this way, clinicians tend to accept these harms as part of the acceptable risk profile for a device.[505] This is not how patients see them, however. Evidence of comparative benefits, particularly comparing how surgical treatment with one device compares with best medical management (or other devices) is often inadequate as device efficacy is often assumed. Therefore, since the data Is unavailable and outcomes are generally unknown, communication does not actually result in increased knowledge, as I had assumed in my conceptual framework.

This means, that we rely on regulation and the rules surrounding medical devices to ensure their safety and efficacy. And as has been seen from the regulation review, this is not the primary intended purpose of EU medical device regulation, so it is unlikely to achieve it, particularly when industry has such an influence on the rules they are regulated by. Furthermore, due to the regulatory harmonisation efforts that have led to a convergence in regulatory practice that closely follows the EU or the US medical device regulatory systems, this is a global issue, not just a national or EU problem.

11.4. Reflexivity

The interpretation of qualitative data requires taking a stance. And taking a stance has the effect of deciding that someone or some group may be more to 'blame' for the lack of patient safety than another, which I've struggled against. My usual stance is to choose to be objective as I feel it is fairer, and I don't wish to be judgemental. However, the attempt to be as balanced as possible and not blame anyone probably delayed my progress, and possibly blinded me to aspects that may be obvious to others[i]. When I realised that qualitative research cannot be completed without taking a position I chose a critical interpretive stance as it fits with my belief that ensuring the safety of medical devices, particularly implantable ones, is a matter of justice, and injustices have to be addressed. Subsequently, the pervasive influence of industry on the regulation of medical devices has slowly dawned on me. In seeking the truth I have tried to be as fair as possible, but still call out the issues and problems that this research exposes.

11.5. Strengths and Limitations

There are several limitations to this research. The limitations regarding the lifecycle review have already been discussed, so this section will focus on the limitations of the regulation review.

As there were no standard methods for exploring legal frameworks from a biomedical and patient safety perspective, this meant that I was constantly developing and refining the methods as I conducted the research, consequently the research process was less focussed than it might have been. However, by focussing on the research methods it is hoped that the study's rigour has been enhanced, and by adopting and adapting different research approaches I have developed a set of processes that I consider to be more appropriate for conducting this type of research.

The research was extensive, taking a long time, which meant that the legal framework continued to evolve, with significant attention being paid to revising it, making it difficult to keep up with the multiplicity of recent legal and policy documents. So, I concentrated my efforts initially on exploring the original legal framework and how it came to be the way it was, tracing its history back to the founding treaties, which may have been an unnecessary detour that detracted from the main focus of the research, which was to understand how the legal framework for medical devices impacted patient safety. Nevertheless, it provided me with a more profound and nuanced insight into the influences on the regulatory process, locally, globally, and historically. Furthermore, it meant a more prolonged engagement with the data, which enabled me to achieve

[i] I had assumed that patient safety mattered to everyone, and that this was more important than other goals.

greater clarity regarding what the 'rules' are (and what they aren't, though we might think they are) and how this has impacted patient safety, and continues to.

11.6. Implications for policy, practice, and future research

There are three main points to be highlighted. First there is insufficient awareness of the problems related to the regulation of medical devices. Secondly, the regulatory framework is inadequate for protecting patients. Thirdly, the evidence base for medical devices is very poor, and is inadequate for evaluating the efficacy or safety of a device. All three of these need to be improved.

11.6.1.1. Lack of awareness of the issues

Policymakers, clinicians, patients, and the public need to be made aware of the fact that CE marking does not mean that a device is either safe or effective. A public information campaign needs to be mounted to highlight this and to demonstrate the need for RCTs as the only valid means of knowing if a device is relatively safe and effective. Since industry will undoubtedly push back against this, with more 'news' regarding the usefulness of RWE and in silico studies, it is crucial that citizens are taught to recognise this for the framing exercise that it is.

11.6.1.2. Regulation needs to be improved

The regulatory process for implantable and other high risk medical devices is not fit for purpose from the perspective of protecting patients or public health. This needs to be addressed by demanding regulation for implantable device with the primary, if not the sole, goal of protecting patients' interests. Therefore, a separate pre-market approval process needs to be established for implantable medical devices that requires clinical evidence derived from RCTs, and a central regulatory authority should be set up to assess all such applications. No implantable device should be excluded from the scope of this new regulation.[i]

In the meantime, the transparency of the clinical data underpinning the current market entry process (i.e. CE marking) for all devices must be improved, specifically the clinical data of approved devices should be made publicly available.

11.6.1.3. The evidence base needs to be improved

There is insufficient evidence regarding the safety and efficacy of practically every implant. Although categories of implant may be considered to be generally safe and

[i] It should include pins, screws, plates, dental implants and any others currently excluded from the scope of the MDR, because all implants require implantation, may cause harm, and can only be removed by explantation, which represents a triple assault on patients in cases where the device is ineffective or causes harm.

effective, individual devices may not be.[506,507] Without the necessary evidence, information on which devices underperform remains unknown until they have significant adverse impacts that garner public attention and/or lead to clinical investigations.

It is imperative, therefore, that healthcare systems don't rely on manufacturers to provide this data. Instead the gathering, collation, analysis, and reporting of clinical outcomes for patients (both receiving and not receiving an implant) should be a routine and ongoing exercise that should be conducted within the healthcare service itself. In this way, the data and the evidence generated from this data is contextualised and relevant to all the key stakeholders, particularly, patients.

11.6.1.4. Specific research needs

Patient preferences regarding 'acceptable risk-benefit'

Manufacturers determine whether the balance between the potential risks and benefits of their device are considered acceptable based on its intended use and indications for use, which they also decide. The evidence underpinning the risk-benefit balance is not available for scrutiny, yet patients and clinicians may not come to the same conclusion as the manufacturer if they had the evidence. Bestowing manufacturers with the right to determine what is an acceptable benefit-risk balance for their own implantable device creates an asymmetry of knowledge and an imbalance of power in determining acceptable levels of risk, between manufacturers and patients that cannot easily be challenged. Consequently, studies eliciting patient preferences regarding what risks they think are acceptable given the expected benefits of a particular type or category of device need to be conducted. Furthermore, the estimation of risks and benefits should be based on rates of actual clinical outcomes (whether gathered in a clinical trial or in a registry), so this data needs to be gathered and analysed for every category of implantable device.

Clinical Investigations

Clinical data underpinning the CE marking is not publicly available. However, there is no legal mandate for confidentiality of published literature and no reason why any published literature used for CE marking should be kept confidential. Therefore, the bibliography supporting an application for CE marking or a clinical investigation should be publicly available.

The results from many clinical trials are not reported. Therefore, each country should introduce sanctions for the non-reporting of clinical trials.

It is likely that informed patient consent to participate in trials is not adequately supported by informing patients of the lack of data on most medical devices, though this is a moot point. However, the lack of appropriate trial design (that omits current best-practice as

treatment for the control group) is an ethical issue that needs addressing. The EU Commission and all individual Member States should sign (and ratify) the Oviedo Convention (see Box 11.1) and its protocols to add legal protection and ensure compliance with the Declaration of Helsinki in clinical trials so that patient rights are upheld.[508]

All clinical investigations of medical devices conducted to obtain CE marking must be reviewed by a Research Ethics Committees (REC) as well as the CA, but without understanding trial methodology as well as the ethical aspects of research, they are at a disadvantage when assessing clinical study designs to determine if they are designed to answer questions of efficacy and safety. Therefore, all REC members should be given standardised training in statistics and epidemiology (as well as ethics) so that they are competent to assess the study protocols presented to them. In particular, it must be impressed upon them that observational data cannot prove causality. Furthermore, all RECs should have access to additional methodological support, particularly for technologies that they are unfamiliar with. Additionally, all RECs should involve actual patients who have the condition in ethical reviews of studies for which the technology is being proposed.

Oviedo Convention and its Protocols

The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: **Convention on Human Rights and Biomedicine** (ETS No 164) was opened for signature on 4 April 1997 in Oviedo (Spain).

This Convention is **the only international legally binding instrument** on the protection of human rights in the biomedical field.

It draws on the principles established by the European Convention on Human Rights, in the field of biology and medicine.

It is a framework Convention aiming at **protecting the dignity and identity of all human beings** and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine.

It sets out fundamental principles applicable to daily medical practice and is regarded as such at the European treaty on patient's rights. It also deals specifically with biomedical research, genetics and transplantation of organ and tissues.

The provisions of the Convention are further elaborated and complemented by Additional Protocols on specific subjects.

Extract from Oviedo Convention and its Protocols. [Internet]. Accessed 2021 Sep 26. Available from: https://www.coe.int/en/web/bioethics/oviedo-convention

Box 11.1. Oviedo Convention on Human Rights and Biomedicine

12. Conclusions

This research sought to identify policy-amenable factors affecting the safety of medical devices from a lifecycle perspective by addressing two research questions:

1. What lifecycle approaches, models or frameworks have been used to evaluate medical devices? What is meant by the 'medical device lifecycle' and 'lifecycle evaluation'? How do these differences in meanings affect patient safety?
2. How are medical devices regulated? How does this affect patient safety?

I found that different actors involved in the lifecycle of a medical device meant different things when referring to the medical device lifecycle and/or lifecycle evaluation. These differences in meaning stemmed from the different goals each group was seeking to achieve, their different evidence needs to fulfil those goals, and consequently, the designing and/or use of the lifecycle evaluation models for different ends. The misunderstanding that these differences engender results in miscommunication (which may sometimes be deliberate) and erroneous assumptions being made, which conceal the motivation underlying the adoption of (or the pressure imposed on others to adopt) a lifecycle approach to evaluation.

The adoption by regulators of a lifecycle approach to regulating medical devices has resulted in the lack of evidence that we see available for evaluating those on the market (justified by the lifecycle premise that this evidence will become available in the post-market phase), which is impacting patients, because it is unclear whether a device is safe and effective or whether it will meet their needs. Succumbing to pressure to adopt a similar approach in healthcare, whereby devices are adopted into the healthcare system with little or no evidence puts patients further at risk of adverse outcomes and it also limits or delays more and better evidence from becoming available. Thus, the research shows that the adoption of a lifecycle approach to evaluating medical devices and the regulatory process itself are key risk factors to medical device safety.

Exploring the regulatory process for medical devices in the EU, I found that there are a plethora of actors involved who each have a role to play in 'regulating' medical devices, but none of these 'regulators' is fully knowledgeable about the devices they are regulating, and they lack power to enforce rules to control the marketing of medical devices[i] because of the fragmented nature of the regulatory structures and processes. Furthermore, the EU's regulatory framework has been designed to benefit industry rather

[i] Though the MDR does strengthen these powers, at least making it easier for NBs and CAs to require manufacturers to implement corrective or preventive measures when a device is shown to be causing more harm than expected. Whether this will lead to them exercising those powers or whether this improves the availability of evidence regarding efficacy, or improves the safety of devices, remains unclear.

than patients' or public interests. Regulation has, in effect, been captured by industry. Furthermore, this has been concealed by framing communications to the public, emphasising the effectiveness of the new, stricter regulation. The result is that calls for regulatory reform have been stemmed, public confidence in medical devices has been restored, and patients continue to have devices implanted into them with an uncertain evidence base, but with greater confidence and peace of mind that the operation will produce a good outcome. Economic operators may complain about the additional rules and obligations that have to be met, but they have less market uncertainty.

This lack of evidence (and potential lack of safety and efficacy) is an injustice to patients and to doctors implanting these products. Healthcare systems should set up the necessary IT systems to systematically capture, clean, curate, collate, appraise, and analyse the necessary data, and disseminate the synthesised evidence to patients, their doctors, and other healthcare providers who need it for clinical decision-making. Preferably before many more people have to suffer, and there is another medical device scandal showing our failure to act.

13. References

1. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices. OJ L 169, 12.7.1993 Jun 14, 1993 p. 1–43.

2. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (Text with EEA relevance.). OJ L 117, 5.5.2017 May 5, 2017 p. 176–332.

3. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. OJ L 117, 5.5.2017 May 5, 2017 p. 1–175.

4. Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices. OJ L 189, 20.7.90 Jul 20, 1990 p. 17–36.

5. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. OJ L 331, 7.12.1998 Oct 27, 1998 p. 1–37.

6. The Implant Files: A global investigation into medical devices [Internet]. ICIJ. [cited 2019 Jan 3]. Available from: https://www.icij.org/investigations/implant-files/

7. Maroo A, Topol EJ. The early history and development of thrombolysis in acute myocardial infarction. Journal of Thrombosis and Haemostasis. 2004 Nov;2(11):1867–70.

8. Tomberli B, Mattesini A, Baldereschi GI, Di Mario C. A Brief History of Coronary Artery Stents. Revista Española de Cardiología (English Edition). 2018 May;71(5):312–9.

9. Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. The Lancet. 2007 Oct;370(9597):1508–19.

10. Wylde V, Learmonth ID, Cavendish VJ. The Oxford hip score: the patient's perspective. Health Qual Life Outcomes. 2005 Oct 31;3:66.

11. Peters W, Pellerin C, Janney C. Evaluation of orthopedic hip device recalls by the FDA from 2007 to 2017. Biomed Instrum Technol. 2020 Nov 1;54(6):418–26.

12. Galhotra S, Maurice J. Assessment of Obstetric and Gynecologic Food and Drug Administration Device Approvals and Recalls. J Minim Invasive Gynecol. 2018 Dec;25(7):1281–8.

13. O'Mahony P, Hanson A. Irish Medicines Board presentation to the Oireachtas Joint Committee on Health & Children on the Depuy ASR(TM) Articular Surface, Replacement and ASR(TM) XL Acetabular System [Internet]. Dublin, Ireland: Irish Medicines Board; 2012 Jul [cited 2018 Feb 4] p. 6. Available from: https://www.oireachtas.ie/parliament/media/committees/healthandchildren/IMB-OpeningStatement_FINAL.pdf

14. Heneghan C, Godlee F. Surgical mesh and patient safety. BMJ (Online). 2018 Oct 10;363(k4231):2.

15. Maijers MC, Niessen FB. The clinical and diagnostic consequences of Poly Implant Prothèse silicone breast implants, recalled from the European market in 2010. Plast Reconstr Surg. 2013 Mar;131(3):394e–402e.

16. Fenoll C, Leclère FM, Hivelin M, Atlan M, Cothier-Savey I, Lantieri L, et al. [Poly Implant Prothèse (PIP®) incidence of complications in breast reconstructive surgery: A retrospective comparative analysis]. Ann Chir Plast Esthet. 2015 Dec;60(6):478–83.

17. Cohen D. Faulty hip implant shows up failings of EU regulation. BMJ. 2012 Oct 23;345:e7163.

18. Cohen D. EU approval system leaves door open for dangerous devices. BMJ. 2012 Oct 24;345:e7173.

19. Campillo-Artero C. A full-fledged overhaul is needed for a risk and value-based regulation of medical devices in Europe. Health Policy. 2013 Nov;113(1–2):38–44.

20. World Health Organization, World Alliance for Patient Safety Research Priority Setting Working Group. Summary of the evidence on patient safety: Implications for research [Internet]. Jha A, editor. Spain: World Health Organization; 2008 [cited 2018 Jan 21]. 138 p. Available from: http://www.who.int/iris/handle/10665/43874

21. McElroy LM, Woods DM, Yanes AF, Skaro AI, Daud A, Curtis T, et al. Applying the WHO conceptual framework for the International Classification for Patient Safety to a surgical population. Int J Qual Health Care. 2016 Apr;28(2):166–74.

22. Runciman W, Hibbert P, Thomson R, Van Der Schaaf T, Sherman H, Lewalle P. Towards an international classification for patient safety: Key concepts and terms. Int J Qual Health Care. 2009 Feb;21(1):18–26.

23. Patient safety [Internet]. 2019 [cited 2019 Jan 15]. Available from: http://www.euro.who.int/en/health-topics/Health-systems/patient-safety

24. WHO | Patient safety [Internet]. WHO. [cited 2017 Mar 20]. Available from: http://www.who.int/patientsafety/en/

25. Samore MH, Evans RS, Lassen A, Gould P, Lloyd J, Gardner RM, et al. Surveillance of medical device-related hazards and adverse events in hospitalized patients. JAMA. 2004 Jan 21;291(3):325–34.

26. HtaGlossary.net | efficacy [Internet]. HtaGlossary.net. [cited 2023 Jan 20]. Available from: http://htaglossary.net/efficacy

27. HtaGlossary.net | effectiveness [Internet]. HtaGlossary.net. [cited 2023 Jan 20]. Available from: http://htaglossary.net/effectiveness

28. Balka E, Doyle-Waters M, Lecznarowicz D, FitzGerald JM. Technology, governance and patient safety: Systems issues in technology and patient safety. Int J Med Inform. 2007;76:S35–47.

29. Horvath G. Trading safety for innovation and access: An empirical evaluation of the FDA's Premarket Approval process. SSRN Journal. 2017;991.

30. Hulstaert F, Pouppez C, Primus-de Jong C, Harkin K, Neyt M. Evidence gaps for drugs and medical devices at market entry in Europe and potential solutions [Internet]. Brussels: Belgian Health Care Knowledge Centre (KCE); 2021 [cited 2021 Dec 17] p. 227. Report No.: KCE Reports 347. D/2021/10.273/45. Available from: https://kce.fgov.be/sites/default/files/atoms/files/KCE_347_Evidence_gaps_Europe_Report_V2.pdf

31. Hulstaert F, Pouppez C, Primus-de Jong C, Harkin K, Neyt M. Gaps in the evidence underpinning high-risk medical devices in Europe at market entry, and potential solutions. Orphanet J Rare Dis. 2023 Dec;18(1):1–13.

32. Laaksonen I, Donahue GS, Madanat R, Makela KT, Malchau H. Outcomes of the Recalled Articular Surface Replacement Metal-on-Metal Hip Implant System: A Systematic Review. J Arthroplasty. 2017 Jan;32(1):341–6.

33. Gross TP, Liu F. Outcomes After Revision of Metal-on-Metal Hip Resurfacing Arthroplasty. The Journal of Arthroplasty. 2014 Sep;29(9):219–23.

34. Demirel F, Adiyaman A, Delnoy PPHM, Smit JJJ, Ramdat Misier AR, Elvan A. Mechanical and electrical dysfunction of Riata implantable cardioverter-defibrillator leads. Europace. 2014 Dec;16(12):1787–94.

35. Hauser RG, Abdelhadi R, McGriff D, Retel LK. Deaths caused by the failure of Riata and Riata ST implantable cardioverter-defibrillator leads. Heart Rhythm. 2012 Aug;9(8):1227–35.

36. Elshaug AG, Moss JR, Littlejohns P, Karnon J, Merlin TL, Hiller JE. Identifying existing health care services that do not provide value for money. Medical Journal of Australia. 2009;190(5):269–73.

37. Audit Commission. Reducing spending on low clinical value treatments. London, England: Audit Commission; 2011 p. 21.

38. Craig A, O'Meley P, Carter P. The need for greater reporting of medical device incidents. EMJ Innov. 2019 Jan;3(1):56–63.

39. Cooper MA, Ibrahim A, Lyu H, Makary MA. Underreporting of robotic surgery complications. J Healthc Qual. 2015 Apr;37(2):133–8.

40. Ibrahim AM, Dimick JB. Monitoring medical devices: Missed warning signs within existing data. JAMA. 2017 Jul 25;318(4):327–8.

41. Bowers S, Cohen D. How lobbying blocked European safety checks for dangerous medical implants. BMJ. 2018 Nov 26;k4999.

42. Hefflin BJ, Gross TP, Schroeder TJ. Estimates of medical device--associated adverse events from emergency departments. Am J Prev Med. 2004 Oct;27(3):246–53.

43. Wang C, Hefflin B, Cope JU, Gross TP, Ritchie MB, Qi Y, et al. Emergency department visits for medical device-associated adverse events among children. Pediatrics. 2010 Aug;126(2):247–59.

44. Myers R, Jones S, Sittig D. Review of Reported Clinical Information System Adverse Events in US Food and Drug Administration Databases. Appl Clin Inform. 2011;02(01):63–74.

45. Brady PW, Varadarajan K, Peterson LE, Lannon C, Gross T. Prevalence and nature of adverse medical device events in hospitalized children. J Hosp Med. 2013 Jul;8(7):390–3.

46. Hwang TJ, Sokolov E, Franklin JM, Kesselheim AS. Comparison of rates of safety issues and reporting of trial outcomes for medical devices approved in the European Union and United States: cohort study. BMJ. 2016 Jun 28;353:i3323.

47. Gagliardi AR, Takata J, Ducey A, Lehoux P, Ross S, Trbovich PL, et al. Medical device recalls in Canada from 2005 to 2015. Int J Technol Assess Health Care. 2017 Jan;33(6):708–14.

48. Madi S, Motara F, Enyuma C, Laher AE. Audit of defibrillators at an urban public sector hospital. Heart Asia. 2018 Aug 17;10(2):e011065.

49. Nackers A, Ehlenbach M, Kelly MM, Werner N, Warner G, Coller RJ. Encounters From Device Complications Among Children With Medical Complexity. Hosp Pediatr. 2019 Jan;9(1):6–15.

50. Palojoki S, Saranto K, Lehtonen L. Reporting medical device safety incidents to regulatory authorities: An analysis and classification of technology-induced errors. Health Informatics J. 2019 Sep;25(3):731–40.

51. Cohen Y, Rallo R, Liu R, Liu HH. In silico analysis of nanomaterials hazard and risk. Acc Chem Res. 2013 Mar 19;46(3):802–12.

52. Altenstetter C. Medical device regulation and nanotechnologies: determining the role of patient safety concerns in policymaking. Law & Policy. 2011 Apr;33(2):227–55.

53. Vinck I, Vijverman A, Vollebregt E, Broeckx N, Wouters K, Piët M, et al. Responsible use of high-risk medical devices: the example of 3D printed medical devices. Brussels: Belgian Health Care Knowledge Centre (KCE); 2018 p. 164. (KCE Reports). Report No.: 297.

54. Schvartzman M, Palma M, Sable J, Abramson J, Hu X, Sheetz MP, et al. Nanolithographic Control of the Spatial Organization of Cellular Adhesion Receptors at the Single-Molecule Level. Nano Lett. 2011 Mar 9;11(3):1306–12.

55. Fernandez-Yague MA, Abbah SA, McNamara L, Zeugolis DI, Pandit A, Biggs MJ. Biomimetic approaches in bone tissue engineering: Integrating biological and physicomechanical strategies. Adv Drug Deliv Rev. 2015 Apr 1;84:1–29.

56. Rauti R, Secomandi N, Martín C, Bosi S, Severino FPU, Scaini D, et al. Tuning Neuronal Circuit Formation in 3D Polymeric Scaffolds by Introducing Graphene at the Bio/Material Interface. Adv Biosyst. 2020;4(4):1900233.

57. Ardaugh B.M., Graves S.E., Redberg R.F. The 510(k) ancestry of a metal-on-metal hip implant. New Engl J Med. 2013 Jan 10;368(2):97–100.

58. Rathi VK, Gadkaree SK, Ross JS, Kozin ED, Sethi RK, Naunheim MR, et al. US Food and Drug Administration Clearance of moderate-risk otolaryngologic devices via the 510(k) process, 1997-2016. Otolaryngol Head Neck Surg. 2017 Oct;157(4):608–17.

59. Stern AD, Kramer DB, Ouellet M, Kesselheim AS. Review times and adverse events for cardiovascular devices. Nat Biomed Eng. 2017 Jan;1(1):0013.

60. Ormstad S, Meyer F, Brühl H. Taking a lifecycle approach to EUnetHTA's work: Current and future collaboration between Early Dialogues and Relative Effectiveness Assessments. [Internet]. 2018 EUnetHTA Forum; 2018 May 5 [cited 2018 Dec 12]; Cologne, Germany. Available from: https://www.eunethta.eu/about-eunethta/2018-eunethta-forum/

61. Home - HTAi 2022 Utrecht Annual Meeting [Internet]. Home. [cited 2023 Feb 3]. Available from: https://www.htai2022.org/htai.eventsair.com

62. Ward JR, Clarkson PJ. An analysis of medical device-related errors: prevalence and possible solutions. J Med Eng Technol. 2004 Feb;28(1):2–21.

63. Zhao P, Li Y, Li Z, Jia P, Zhang L, Zhang M. Use of patient safety culture instruments in operating rooms: A systematic literature review. J Evid-Based Med. 2017;10(2):145–51.

64. Commission on Patient Safety and Quality Assurance. Building a culture of patient safety [Internet]. Dublin, Ireland: Commission on Patient Safety and Quality Assurance; 2008 Jul p. 241. Available from: http://health.gov.ie/wp-content/uploads/2014/03/en_patientsafety.pdf

65. Culture of Safety | AHRQ Patient Safety Network [Internet]. [cited 2018 Aug 7]. Available from: https://psnet.ahrq.gov/primers/primer/5/culture-of-safety

66. Mathias JM. Stryker's Neptune recall raises stakes for compliance. OR Manager. 2013 May;29(5):16–7.

67. O'Dowd A. UK recommends PIP breast implants should not be removed. BMJ. 2011 Dec 22;343:d8313.

68. Edlich RF, Garrison JA, Nearents JE. The FDA agrees to ban powdered medical and surgical gloves. J Emerg Med. 2014 Mar;46(3):e105-106.

69. ECRI Institute offers recommendations on Cardiac Science AED recall. Health Devices. 2010 Jul;39(7):253–5.

70. FDA and Baxter announce details of colleague infusion pump recall. Health Devices. 2010 Aug;39(8):294–5.

71. Hospitals should begin removing certain interpower power cords from service. Health Devices. 2010 Feb;39(2):62–4.

72. Heneghan C, Langton D, Thompson M. Ongoing problems with metal-on-metal hip implants. BMJ. 2012 Feb 28;344:e1349.

73. Chalmers I. Trying to do more good than harm in policy and practice: The role of rigorous, transparent, up-to-date evaluations. Ann Am Acad Pol Soc Sci. 2003 Sep;589(1):22–40.

74. Glasziou PP, Chris DM, Salisbury J. Evidence-Based Practice Workbook. 2nd ed. Malden, Mass. Oxford: BMJ Books; 2007. 208 p.

75. Hulstaert F, Neyt M, Vinck I, Stordeur S, Huić M, Sauerland S, et al. Pre-market clinical evaluations of innovative high-risk medical devices in Europe. Int J Technol Assess Health Care. 2012 Jul;28(3):278–84.

76. McKinlay JB. From promising report to standard procedure: Seven stages in the career of a medical innovation. Milbank Mem Fund Q Health Soc. 1981;59(3):374–411.

77. Wild C, Erdös J, Zechmeister I. Contrasting clinical evidence for market authorisation of cardio-vascular devices in Europe and the USA: A systematic analysis of 10 devices based on Austrian pre-reimbursement assessments. BMC Cardiovasc Disord. 2014 Nov 4;14(1):154.

78. Tarricone R, Torbica A, Drummond M. Challenges in the Assessment of Medical Devices: The MedtecHTA Project. Health Econ. 2017 Feb 1;26 Suppl 1:5–12.

79. Drummond M, Griffin A, Tarricone R. Economic evaluation for devices and drugs--same or different? Value Health. 2009 Jun;12(4):402–4.

80. Wilkinson B, van Boxtel R. The Medical Device Regulation of the European Union Intensifies Focus on Clinical Benefits of Devices. Therapeutic Innovation & Regulatory Science. 2020 Jun;54(3):613–7.

81. Alsagheir A, Koziarz A, Belley-Côté EP, Whitlock RP. Expertise-based design in surgical trials: a narrative review. Can J Surg. 2021;64(6):E594–602.

82. Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT. Statistical assessment of the learning curves of health technologies. Health Technol Assess. 2001;5(12):1–79.

83. Sauerland S, Fujita-Rohwerder N, Zens Y, Molnar S. Premarket evaluation of medical devices: A cross-sectional analysis of clinical studies submitted to a German ethics committee. BMJ Open. 2019 Feb 22;9(2):e027041.

84. Fraser AG, Butchart EG, Szymański P, Caiani EG, Crosby S, Kearney P, et al. The need for transparency of clinical evidence for medical devices in Europe. Lancet. 2018 Aug 11;392(10146):521–30.

85. Fujita-Rohwerder N, Sauerland S. Bewertung von Medizinprodukten auf europäischer Ebene gemäß der neuen HTA-Verordnung (HTAR) – welche Evidenz erwartet uns? In: Health and climate – EbM for the future [Internet]. Potsdam, Germany.: German Medical Science GMS Publishing House; 2023 [cited 2023 Dec 20]. p. Doc23ebmPSI-4–02. Available from: https://www.egms.de/static/de/meetings/ebm2023/23ebm052.shtml

86. Rathi VK, Krumholz HM, Masoudi FA, Ross JS. Characteristics of clinical studies conducted over the total product life cycle of high-risk therapeutic medical devices receiving FDA Premarket approval in 2010 and 2011. JAMA. 2015 Aug 11;314(6):604–12.

87. Gagliardi AR, Ducey A, Lehoux P, Turgeon T, Ross S, Trbovich P, et al. Factors influencing the reporting of adverse medical device events: qualitative interviews with physicians about higher risk implantable devices. BMJ Qual Saf. 2018 Mar;27(3):190–8.

88. Harris C, Allen K, Waller C, Brooke V. Sustainability in health care by allocating resources effectively (SHARE) 3: examining how resource allocation decisions are made, implemented and evaluated in a local healthcare setting. BMC Health Serv Res. 2017 Dec;17(1):340.

89. Hauser RG. Here we go again — Another failure of postmarketing device surveillance. N Engl J Med. 2012 Mar 8;366(10):873–5.

90. Reason J. Too little and too late: A commentary on accident and incident reporting systems. In: van der Schaaf TW, Lucar DA, Hale AR, editors Near Miss Reporting As a Safety Tool [Internet]. Elsevier; 1991 [cited 2021 Jan 3]. p. 9–26. Available from: https://linkinghub.elsevier.com/retrieve/pii/B978075061178750006X

91. Reason J. Understanding adverse events: Human factors. Qual Health Care. 1995 Jun;4(2):80–9.

92. Reason J. Human error: Models and management. BMJ. 2000 Mar 18;320(7237):768–70.

93. System Safety Handbook [Internet]. [cited 2021 May 11]. Available from: https://www.faa.gov/regulations_policies/handbooks_manuals/aviation/risk_management/ss_handbook/

94. HSE Investigation Processes Working Group Chaired by Ms. Cora McCaughan. HSE Guidelines for the Systems Analysis Investigation of Incidents. Part 1 and Part 2 [Internet]. Health Service Executive (HSE); 2016 [cited 2018 Jan 16]. Available from: https://www2.healthservice.hse.ie/organisation/qps-incident-management/

95. Pane J, Verhamme KMC, Villegas D, Gamez L, Rebollo I, Sturkenboom MCJM. Challenges associated with the safety signal detection process for medical devices. Med Devices Evid Res. 2021;14:43–57.

96. Mytton OT, Velazquez A, Banken R, Mathew JL, Ikonen TS, Taylor K, et al. Introducing new technology safely. Qual Saf Health Care. 2010 Aug;19 Suppl 2:i9-14.

97. Cheng M. Medical device regulations: Global overview and guiding principles. Geneva: World Health Organization; 2003. 43 p.

98. Batalden PB, Davidoff F. What is ‘quality improvement’ and how can it transform healthcare? Qual Saf Health Care. 2007 Feb 1;16(1):2–3.

99. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AHS, Dellinger EP, et al. A Surgical Safety Checklist to Reduce Morbidity and Mortality in a Global Population. New England Journal of Medicine. 2009 Jan 29;360(5):491–9.

100. Kovoor JG, Bacchi S, Gupta AK, O’Callaghan PG, Trochsler MI, Maddern GJ. Standardizing optimization in surgery. ANZ Journal of Surgery [Internet]. [cited 2022 Dec 31];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/ans.18201

101. Temple-Bird C, Kaur M, Lenel A, Kawohl W. How to operate your healthcare technology effectively and safely. St Albans: Teaching-aids At Low Cost; 2005. 245 p. (‘How to Manage’ Series for Healthcare Technology).

102. Worm A. Managing the lifecycle of medical equipment [Internet]. London, England: Tropical Health and Education Trust (THET); 2015 Sep [cited 2018 Jan 9] p. 12. Available from: https://www.thet.org/wp-content/uploads/2017/08/THET_Managing_the_medical_equipment_lifecycle_LOW-RES.pdf

103. World Health Organization. Development of medical device policies [Internet]. Geneva, Switzerland: World Health Organization; 2011. 39 p. (WHO medical device technical series). Available from: http://apps.who.int/medicinedocs/documents/s21559en/s21559en.pdf?ua=1

104. Management and Use [Internet]. [cited 2022 Dec 31]. Available from: https://www.who.int/teams/health-product-policy-and-standards/assistive-and-medical-technology/medical-devices/management-use

105. World Health Organization, editor. Needs assessment for medical devices. Geneva, Switzerland: World Health Organization; 2011. 25 p. (WHO medical device technical series/Série technique de l’OMS sur les dispositifs médicaux).

106. World Health Organization, editor. Procurement process resource guide. Geneva, Switzerland: World Health Organization; 2011. 32 p. (WHO medical device technical series).

107. World Health Organization. Health technology assessment of medical devices [Internet]. Geneva, Switzerland: World Health Organization; 2011 [cited 2016 Mar 15] p. 44. (WHO Medical Device Technical Series: To Ensure Improved Access, Quality and Use of Medical Devices). Report No.: 11. Available from: http://apps.who.int/iris/bitstream/10665/44564/1/9789241501361_eng.pdf

108. World Health Organization. WHO global model regulatory framework for medical devices including in vitro diagnostic medical devices [Internet]. Geneva: World Health Organization; 2017. 76 p. (WHO Medical device technical series). Available from: https://apps.who.int/iris/bitstream/handle/10665/255177/9789241512350-eng.pdf?sequence=1

109. Velazquez-Berumen A, David Y, Rogers P, MacDonald R. Development of medical device policies [Internet]. Geneva, Switzerland: World Health Organization; 2011 Jun p. 45. (WHO Medical Device Technical Series: To Ensure Improved Access, Quality and Use of Medical Devices). Available from: http://apps.who.int/medicinedocs/documents/s21559en/s21559en.pdf?ua=1

110. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: The IDEAL recommendations. Lancet. 2009 Sep 26;374(9695):1105–12.

111. Pennell CP, Hirst A, Sedrakyan A, McCulloch PG. Adapting the IDEAL Framework and Recommendations for medical device evaluation: A modified Delphi survey. Int J Surg. 2016 Apr;28:141–8.

112. Sedrakyan A, Campbell B, Merino JG, Kuntz R, Hirst A, McCulloch P. IDEAL-D: A rational framework for evaluating and regulating the use of medical devices. BMJ. 2016 Jun 9;353:i2372.

113. Taylor BJ, Francis K. Qualitative research in the health sciences: Methodologies, methods, and processes. Milton Park, Abingdon, Oxon ; New York, NY: Routledge; 2013. 297 p.

114. Creswell JW, Creswell JD. Research design: Qualitative, quantitative, and mixed methods approaches. 5th edition, international student edition. Los Angeles London New Delhi Singapore Washington DC Melbourne: SAGE; 2018. 275 p.

115. Strauss A, Corbin J. Basics of qualitative research: Techniques and procedures for developing grounded theory. 2nd ed. Thousand Oaks: Sage Publications; 1998. 336 p.

116. Creswell JW, Creswell JD. Research Design: Qualitative, Quantitative, and Mixed Methods Approaches. Fifth Edition. Los Angeles London New Delhi Singapore Washington DC Melbourne: SAGE Publications, Inc; 2018. 304 p.

117. Greenhalgh T, Annandale E, Ashcroft R, Barlow J, Black N, Bleakley A, et al. An open letter to The BMJ editors on qualitative research. BMJ. 2016 Feb 10;i563.

118. Wong G. Knowledge synthesis approaches–spoilt for choice? J Clin Epidemiol. 2016 May;73:8–10.

119. Mays N, Pope C, Popay J. Systematically reviewing qualitative and quantitative evidence to inform management and policy-making in the health field. J Health Serv Res Policy. 2005 Jul;10 Suppl 1:6–20.

120. Petticrew M, Rehfuess E, Noyes J, Higgins JPT, Mayhew A, Pantoja T, et al. Synthesizing evidence on complex interventions: how meta-analytical, qualitative, and mixed-method approaches can contribute. J Clin Epidemiol. 2013 Nov;66(11):1230–43.

121. Pawson R, Greenhalgh T, Harvey G, Walshe K. Realist review--a new method of systematic review designed for complex policy interventions. J Health Serv Res Policy. 2005 Jul;10 Suppl 1:21–34.

122. Pope C, Mays N. Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. BMJ. 1995 Jul 1;311(6996):42–5.

123. Rogers EM. Diffusion of innovations. 5th ed. New York: Free Press; 2003. 551 p.

124. Bowling A. Research methods in health: investigating health and health services. 2nd ed. Buckingham ; Philadelphia: Open University Press; 2002. 486 p.

125. Levitt HM. Qualitative generalization, not to the population but to the phenomenon: Reconceptualizing variation in qualitative research. Qual Psychol. 2021 Feb;8(1):95–110.

126. Lincoln YS, Guba EG. But is it rigorous? Trustworthiness and authenticity in naturalistic evaluation. New Dir Program Eval. 1986;1986(30):73–84.

127. Qin D. Positionality. In: The Wiley Blackwell Encyclopedia of Gender and Sexuality Studies [Internet]. American Cancer Society; 2016 [cited 2021 Jan 14]. p. 1–2. Available from: http://onlinelibrary.wiley.com/doi/abs/10.1002/9781118663219.wbegss619

128. Jafar AJN. What is positionality and should it be expressed in quantitative studies? Emerg Med J. 2018 Jan 11;emermed-2017-207158.

129. Rowe WE. Positionality. In: Coughlan D, Brydon-Miller M, editors. The SAGE Encyclopedia of Action Research [Internet]. London, United Kingdom: SAGE Publications; 2014 [cited 2021 Jan 5]. p. 627–8. Available from: http://ebookcentral.proquest.com/lib/trinitycollege/detail.action?docID=1712670

130. Harkin K. A mini-HTA: The Propulse NG for ear irrigation at the School Hearing Clinic. Sligo, Ireland: Community Medicine Department, Community Services, HSE, Sligo; 2013 p. 33.

131. Harkin K. Health Technology Assessment of scheduled procedures: Hip replacement for end-stage osteoarthritis of the hip [Master Thesis]. [Barcelona]: University of Barcelona; 2014.

132. Harkin K, Dee A. PP66 Hospital cleaning: Detergent or disinfectant-detergent? A rapid review. International Journal of Technology Assessment in Health Care. 2018;34(S1):92–3.

133. Thorne S, Kirkham SR, MacDonald-Emes J. Interpretive description: A noncategorical qualitative alternative for developing nursing knowledge. Res Nurs Health. 1997 Apr;20(2):169–77.

134. Kaplan G, Bo-Linn G, Carayon P, Pronovost P, Rouse W, Reid P, et al. Bringing a systems approach to health [Internet]. Washington DC: Discussion Paper, Institute of Medicine and National Academy of Engineering; 2013 Jul [cited 2023 Jan 22] p. 26. Available from: https://nam.edu/perspectives-2013-bringing-a-systems-approach-to-health/

135. Wolf ZR, Hughes RG. Error Reporting and Disclosure. In: Hughes RG, editor. Patient Safety and Quality: An Evidence-Based Handbook for Nurses [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008 [cited 2022 Feb 17]. (Advances in Patient Safety). Available from: http://www.ncbi.nlm.nih.gov/books/NBK2652/

136. Green MD, Freedman DM, Gordis L. Reference guide on epidemiology. In: Reference Manual on Scientific Evidence: Second Edition [Internet]. Washington DC: National Academies Press; 2011 [cited 2022 Mar 30]. p. 333–400. Available from: http://www.nap.edu/read/13163/chapter/12

137. Rogers EM. Diffusion of innovations. 3rd ed. New York : London: Free Press ; Collier Macmillan; 1983. 453 p.

138. Alderson P. The importance of theories in health care. BMJ. 1998;317:1007–10.

139. Ravitch SM, Carl NM. Chapter Two: Conceptual frameworks in research. In: Ravitch SM, Carl NM, authors Qualitative research: Bridging the conceptual, theoretical, and methodological. Second. SAGE Publications; 2019. p. 32–61.

140. Altenstetter C. Medical devices: European Union policymaking and the implementation of health and patient safety in France. London and New York: Routledge. First published by Transaction Publishers; 2008. 304 p.

141. Van Norman GA. Drugs and devices: Comparison of European and US approval processes. J Am Coll Cardiol Basic Trans Science. 2016 Aug 1;1(5):399–412.

142. Baldwin R, Cave M, Lodge M. Understanding regulation: Theory, strategy, and practice [Internet]. 2nd ed. Understanding Regulation. Oxford: Oxford University Press; 2012 [cited 2020 Apr 27]. 548 p. Available from: https://www.oxfordscholarship.com/view/10.1093/acprof:osobl/9780199576081.001.0001/acprof-9780199576081

143. Coglianese C. Measuring Regulatory Policy: Evaluating the impact of regulation and regulatory policy [Internet]. Operation for Economic Cooperation and Development (OECD); 2012 Aug [cited 2019 Jul 2] p. 59. Report No.: 1. Available from: https://www.oecd.org/gov/regulatory-policy/1_coglianese%20web.pdf

144. Coglianese C. Regulation's Four Core Components [Internet]. The Regulatory Review. 2012 [cited 2020 Feb 19]. Available from: https://www.theregreview.org/2012/09/17/regulations-four-core-components/

145. Stigler GJ. The Theory of Economic Regulation. Bell J Econ & Manage Sci. 1971;2(1):3.

146. EEA Agreement | European Free Trade Association [Internet]. [cited 2020 May 17]. Available from: https://www.efta.int/eea/eea-agreement

147. den Hertog JA. Review of economic theories of regulation [Internet]. Utrecht School of Economics; 2010 Dec [cited 2020 Apr 27]. Report No.: 10–18. Available from: https://econpapers.repec.org/paper/usetkiwps/1018.htm

148. Donaldson C, Gerard K. Economics of health care financing: the visible hand. Basingstoke: The Macmillan Press Ltd; 1993. 217 p. (Economic issues in health care).

149. Baldwin R, Cave M, Lodge M. Why regulate? In: Baldwin R, Cave M, Lodge M, editors. Understanding regulation: theory, strategy, and practice. 2nd ed. Oxford: Oxford University Press; 2012.

150. Posner RA. Theories of economic regulation. Bell J Econ. 1974;5(2):335–58.

151. Bounds S. The four types of regulation [Internet]. knowquestion :: Stephen Bounds. Organisations & communities in the knowledge age. [cited 2020 Feb 17]. Available from: http://bounds.net.au/node/65

152. Agence Nationale de Sécurité de Médicament et des Produits de Santé (ANSM). Surgical mesh implants for treatment of urinary incontinence and pelvic organ prolapse. ANSM review of French market between 2014 and 2017 [Internet]. Paris, France: Agence Nationale de Sécurité de Médicament et des Produits de Santé (ANSM); 2018 Nov p. 17. Available from: https://ansm.sante.fr/uploads/2020/10/30/20201030-rapport-mesh-version-gb-2019-01-04.pdf

153. Sertkaya A, DeVries R, Jessup A, Beleche T. Estimated Cost of Developing a Therapeutic Complex Medical Device in the US. JAMA Netw Open. 2022 Sep 14;5(9):e2231609.

154. Pietzsch JB, Shluzas LA, Paté-Cornell ME, Yock PG, Linehan JH. Stage-gate process for the development of medical devices. J Med Devices. 2009 Jun 1;3(2):021004.

155. Greek Medicine - The Hippocratic Oath [Internet]. U.S. National Library of Medicine; [cited 2020 Aug 12]. Available from: https://www.nlm.nih.gov/hmd/greek/greek_oath.html

156. Beauchamp TL, Childress JF. Principles of Biomedical Ethics. Oxford University Press; 2009. 417 p.

157. Gillon R. Defending the four principles approach as a good basis for good medical practice and therefore for good medical ethics. Journal of Medical Ethics. 2015 Jan 1;41(1):111–6.

158. Guide to Professional Conduct and Behaviour for Registered Medical Practitioners [Internet]. [cited 2018 Jan 17]. Available from: https://www.medicalcouncil.ie/News-and-Publications/Publications/Professional-Conduct-Ethics/Guide-to-Professional-Conduct-and-Behaviour-for-Registered-Medical-Practitioners-pdf.pdf

159. Harris IA, Buchbinder R. How doctors are betraying the Hippocratic oath. BMJ. 2021 Nov 16;375:n2807.

160. Hirshorn SR, Voss LD, Bromley LK. NASA System Engineering Handbook NASA/SP-2016-6105 Rev 2 [Internet]. United States: National Aeronautics and Space Administration; 2017 [cited 2018 Nov 26]. 356 p. Available from: https://strives-uploads-prod.s3.us-gov-west-1.amazonaws.com/20170001761/20170001761.pdf?AWSAccessKeyId=AKIASEVSKC45ZTTM42XZ&Expires=1597269250&Signature=UcmT%2FsTd8llugGmLetKdqHHPleA%3D

161. Implementation - Legislation - Environment - European Commission [Internet]. European Commission. 2020 [cited 2020 Aug 13]. Available from: https://ec.europa.eu/environment/legal/implementation_en.htm

162. Litan R. Regulation [Internet]. Econlib. [cited 2020 Feb 17]. Available from: https://www.econlib.org/library/Enc/Regulation.html

163. Windholz E, Hodge G. Conceptualising Social and Economic Regulation: Implications for Modern Regulators and Regulatory Activity [Internet]. Rochester, NY: Social Science Research Network; 2012 [cited 2020 Aug 13]. Report No.: ID 2215334. Available from: https://papers.ssrn.com/abstract=2215334

164. Pritchett W. Types of regulation [Internet]. The Regulatory Review: A Publication of the Penn Program on Regulation. 2016 [cited 2020 Feb 19]. Available from: https://www.theregreview.org/2016/04/05/pritchett-types-of-regulation/

165. Medical Product Alert N°3/2020 [Internet]. [cited 2020 Aug 13]. Available from: https://www.who.int/news-room/detail/31-03-2020-medical-product-alert-n-3-2020

166. WHO Information Notice for Users of Medical Devices 2020/3 [Internet]. [cited 2020 Aug 13]. Available from: https://www.who.int/news-room/detail/07-08-2020-who-information-notice-for-users-of-medical-devices-2020-3

167. Substandard and falsified medical products [Internet]. [cited 2020 Aug 13]. Available from: https://www.who.int/westernpacific/health-topics/substandard-and-falsified-medical-products

168. United Nations Millennium Development Goals [Internet]. United Nations; [cited 2020 May 8]. Available from: https://www.un.org/millenniumgoals/

169. International Trade Agreements [Internet]. Econlib. [cited 2020 May 8]. Available from: https://www.econlib.org/library/Enc/InternationalTradeAgreements.html

170. WTO | Aid for Trade - gateway [Internet]. [cited 2020 May 8]. Available from: https://www.wto.org/english/tratop_e/devel_e/a4t_e/aid4trade_e.htm

171. World Trade Organization. Aid-for-trade workshop - 'Transformation and promoting rural economy' [Internet]. [cited 2020 May 8]. Available from: https://www.wto.org/english/tratop_e/devel_e/a4t_e/a4twkshp_11022020_e/a4twkshp_11022020_e.htm

172. Health Product Policy and Standards. Annex 3. WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices. In: WHO, editor WHO Expert Committee on Biological Standardization Seventy-sixth report [Internet]. Geneva, Switzerland: World Health Organization; 2023 [cited 2023 Jul 14]. p. 179–325. Available from: https://www.who.int/publications/i/item/9789240074484

173. INTEGRATE-HTA Consortium. Results of the INTEGRATE-HTA project [Internet]. INTEGRATE-HTA. 2016 [cited 2020 Dec 23]. Available from: http://www.integrate-hta.eu/downloads/

174. Campbell M, Egan M, Lorenc T, Bond L, Popham F, Fenton C, et al. Considering methodological options for reviews of theory: Illustrated by a review of theories linking income and health. Syst Rev. 2014 Oct 13;3:114.

175. Jackson T. Motivating Sustainable Consumption: A Review of Evidence on Consumer Behaviour and Behavioural Change : a Report to the Sustainable Development Research Network. Centre for Environmental Strategy; 2005. 154 p.

176. Gough D, Thomas J, Oliver S. Clarifying differences between review designs and methods. Syst Rev. 2012 Jun 9;1(1):28.

177. Garside R, White 7 October 2020. The methods and role for qualitative evidence synthesis [Internet]. Webinar presented at: The methods and role for qualitative evidence synthesis; 2020 Oct 7 [cited 2021 Jun 15]; Online. Available from: https://www.youtube.com/watch?v=17-Npni61Zc

178. Carroll C. Qualitative evidence synthesis to improve implementation of clinical guidelines. BMJ. 2017 Jan 16;356:j80.

179. Bowen GA. Document analysis as a qualitative research method. Qualitative Research Journal. 2009 Aug 3;9(2):27–40.

180. Pandit NR. The creation of theory: A recent application of the Grounded Theory method. Qual Rep. 1996 Dec;2(4):1–15.

181. Caulley DN. Document analysis in program evaluation. Eval Program Plann. 1983 Jan 1;6(1):19–29.

182. Schnell-Inderst P, Mayer J, Lauterberg J, Hunger T, Arvandi M, Conrads-Frank A, et al. Health technology assessment of medical devices: What is different? An overview of three European projects. Z Evid Fortbild Qual Gesundhwes. 2015;109(4–5):309–18.

183. Rothery C, Claxton K, Palmer S, Epstein D, Tarricone R, Sculpher M. Characterising Uncertainty in the Assessment of Medical Devices and Determining Future Research Needs. Health Econ. 2017 Feb 1;26 Suppl 1:109–23.

184. Nilsen P. Making sense of implementation theories, models and frameworks. Implement Sci. 2015 Apr 21;10(1):53.

185. Michie S, van Stralen MM, West R. The behaviour change wheel: A new method for characterising and designing behaviour change interventions. Implement Sci. 2011 Apr 23;6(1):42.

186. Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol. 2012 Nov 27;12:181.

187. Booth A, Carroll C. Systematic searching for theory to inform systematic reviews: Is it feasible? Is it desirable? Health Info Libr J. 2015;32(3):220–35.

188. Cooper C, Lovell R, Husk K, Booth A, Garside R. Supplementary search methods were more effective and offered better value than bibliographic database searching: A case study from public health and environmental enhancement. Res Synth Methods. 2018 Jun;9(2):195–223.

189. Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: Audit of primary sources. Br Med J. 2005 Nov 5;331(7524):1064–5.

190. D'Amour D, Ferrada-Videla M, San Martin Rodriguez L, Beaulieu MD. The conceptual basis for interprofessional collaboration: Core concepts and theoretical frameworks. J Interprof Care. 2005 May;19 Suppl 1:116–31.

191. Garside R. Should we appraise the quality of qualitative research reports for systematic reviews, and if so, how? Innovation. 2014 Jan 2;27(1):67–79.

192. Booth A. ESQUIRE Day Two – Selecting, extracting, assessing and synthesising data. ScHARR Short Course presented at: Evidence Synthesis of Qualitative Research in Europe (ESQUIRE) 2018; 2018 Sep 12; Halifax Hall Hotel & Conference Centre, Endcliffe Vale Road, Sheffield, University of Sheffield.

193. Barnett-Page E, Thomas J. Methods for the synthesis of qualitative research: A critical review. BMC Medical Research Methodology [Internet]. 2009 Dec [cited 2017 Jul 12];9(1). Available from: http://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-9-59

194. Erlingsson C, Brysiewicz P. A hands-on guide to doing content analysis. African Journal of Emergency Medicine. 2017 Sep 1;7(3):93–9.

195. France E, Jepson R. What is qualitative evidence synthesis and what is meta-ethnography? [Internet]. 2015 Dec; online. Available from: https://emergeproject.org/wp-content/uploads/2016/10/MetaethnographyForNovice.pdf

196. France EF, Uny I, Ring N, Turley RL, Maxwell M, Duncan EAS, et al. A methodological systematic review of meta-ethnography conduct to articulate the complex analytical phases. BMC Med Res Methodol. 2019 Feb 18;19(1):35.

197. Hard N, Lee P, Dockett S. Mapping the Policy Landscape of Australian Early Childhood Education Policy through Document Analysis. Australasian Journal of Early Childhood. 2018 Jun;43(2):4–13.

198. Wesley JJ. Qualitative Document Analysis in Political Science. :15.

199. Owen GT. Qualitative Methods in Higher Education Policy Analysis: Using Interviews and Document Analysis. 2014;19.

200. Cardno C. Policy Document Analysis: A Practical Educational Leadership Tool and a Qualitative Research Method. Educational Administration: Theory and Practice. 2019 Jan 15;24(4):623–40.

201. About Us - CÚRAM [Internet]. [cited 2021 Mar 5]. Available from: http://curamdevices.ie/curam/about-us/

202. ONLINE CRDI Course: Fundamentals in Medical Device Design and Regulation [Internet]. Clinical Research Development Ireland. [cited 2020 Jul 22]. Available from: https://crdi.ie/education/courses/online-crdi-course-fundamentals-medical-device-design-regulation-gen/

203. EU law - EUR-Lex [Internet]. [cited 2020 Jul 28]. Available from: https://eur-lex.europa.eu/homepage.html

204. Frequently asked questions - EUR-Lex [Internet]. [cited 2020 Jun 30]. Available from: https://eur-lex.europa.eu/content/help/faq/intro.html

205. CheckLex [Internet]. [cited 2020 Jul 23]. Available from: https://checklex.publications.europa.eu/?lang=en

206. Whois result - eir.ie [Internet]. IE Domain Registry. [cited 2020 Jul 30]. Available from: https://www.iedr.ie/whois-result/

207. Whois result - oireachtas.ie [Internet]. IE Domain Registry. [cited 2020 Jul 29]. Available from: https://www.iedr.ie/whois-result/

208. Whois result - hpra.ie [Internet]. IE Domain Registry. [cited 2020 Jul 30]. Available from: https://www.iedr.ie/whois-result/

209. Whois result - nsai.ie [Internet]. IE Domain Registry. [cited 2020 Jul 30]. Available from: https://www.iedr.ie/whois-result/

210. Consolidated version of the Treaty on the Functioning of the European Union [Internet]. European Union; 2012 [cited 2020 Jan 8]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:C:2012:326:FULL&from=EN

211. Court of Justice of the European Union (CJEU) - Overview [Internet]. European Union. 2016 [cited 2021 Mar 8]. Available from: https://europa.eu/european-union/about-eu/institutions-bodies/court-justice_en

212. Farmer T, Robinson K, Elliott SJ, Eyles J. Developing and implementing a triangulation protocol for qualitative health research. Qual Health Res. 2006 Mar 1;16(3):377–94.

213. Ponterotto J. Brief note on the origins, evolution, and meaning of the qualitative research concept thick description. TQR [Internet]. 2015 Jan 16 [cited 2023 Jul 28]; Available from: https://nsuworks.nova.edu/tqr/vol11/iss3/6/

214. Notified Bodies Operations Group (NBOG). NBOG's Best Practice Guide: Certificates issued by Notified Bodies with reference to Council Directives – 93/42/EEC on medical devices (MDD) – 98/79/EC on in vitro diagnostic medical devices (IVDD) – 90/385/EEC on active implantable medical devices (AIMDD) [Internet]. 2010 [cited 2020 Feb 14]. Available from: http://www.doks.nbog.eu/Doks/NBOG_BPG_2010_3.pdf

215. European Commission. Commission notice, The 'Blue Guide' on the implementation of EU products rules 2016 [Internet]. OJ C 272, 26.7.2016 Jul 26, 2016 p. 156. Available from: https://ec.europa.eu/growth/content/%E2%80%98blue-guide%E2%80%99-implementation-eu-product-rules-0_en

216. Berg BL. Chapter 9. Historiography and Oral Traditions. In: Berg BL Qualitative research methods for the social sciences. 4th ed. Boston: Allyn and Bacon; 2001. p. 210–24.

217. Sandelowski M. Whatever happened to qualitative description? Res Nurs Health. 2000 Aug;23(4):334–40.

218. Rostow WW. Kondratieff, Schumpeter, and Kuznets: Trend periods revisited. The Journal of Economic History. 1975 Dec;35(04):719–53.

219. Jovanovic B. Michael Gort's Contribution to Economics. Review of Economic Dynamics. 1998;1(2):327–37.

220. Kuznets S. Secular movements in production and prices: Their nature and their bearing upon cyclical fluctuations. A. M. Kelley; 1967. 576 p.

221. Ryan B, Gross N. Acceptance and diffusion of hybrid corn seed in two Iowa communities. Research Bulletin. 1950 Jan;29(No.327, Article 1):661–708.

222. Ryan B, Gross NC. The Diffusion of Hybrid Seed Corn In Two Iowa Communities. Rural Sociology. 1943;8(1):15–24.

223. Baldock AL. How to introduce a new product. In: 1960 EI National Conference on the Application of Electrical Insulation. 1960. p. 171–2.

224. Levitt T. Exploit the Product Life Cycle. Harv Bus Rev. 1965 Nov 1;43(6):81–94.

225. Bass FM. A new product growth for model consumer durables. Manage Sci. 2004 Dec;50(12_supplement):1825–32.

226. Bass FM. A dynamic model of market share and sales behavior. In: Winter Conference [Internet]. Chicago, IL; 1963 [cited 2020 Jan 19]. p. 263–76. Available from: http://www.bassbasement.org/F/N/FMB/Pubs/Bass%201963%20Dynamic%20Model.pdf

227. Yin RK. Life histories of innovations: How new practices become routinized. Public Adm Rev. 1981;41(1):21–8.

228. Fortenberry Jr JL. Booz, Allen, and Hamilton's new product process. In: John L Fortenberry Jr Nonprofit Marketing [Internet]. Jones & Bartlett Publishers; 2013. p. 11–8. Available from: https://books.google.ie/books?id=0AFwbnQrm7wC&printsec=frontcover&source=gbs_ge_summary_r&cad=0#v=onepage&q&f=false

229. Booz, Allen, Hamilton. New products management for the 1980s. New York: Booz, Allen and Hamilton Inc; 1982. 24 p.

230. Galbraith J. The stages of growth. J Bus Strategy. 1982 Summer;3(000001):70–9.

231. Klepper S. Entry, exit, growth, and innovation over the Product Life Cycle. Am Econ Rev. 1996;86(3):562–83.

232. Gort M, Klepper S. Time paths in the diffusion of product innovations. Econ J (London). 1982 Sep;92(367):630.

233. Klepper S. Industry life cycles. Ind Corp Chang. 1997 Jan 1;6(1):145–82.

234. Cooper RG, Kleinschmidt EJ. An investigation into the new product process: Steps, deficiencies, and impact. J Prod Innov Manag. 1986 Jun 1;3(2):71–85.

235. Norton JA, Bass FM. A diffusion theory model of adoption and substitution for successive generations of high-technology products. Manage Sci. 1987 Sep 1;33(9):1069–87.

236. Cooper RG. Stage-gate systems: A new tool for managing new products. Bus Horiz. 1990 May 1;33(3):44–54.

237. Balakrishnan S. Strategies for High-Tech Markets. Based on Inside the Tornado (by Geoffrey A. Moore) [Internet]. Lecture presented at; [cited 2020 Jan 14]; University of Washington. Available from: http://faculty.washington.edu/sundar/NPM/LECTURE-PDF/S%2316b-TALC-Handout.pdf

238. Moore GA. Crossing the chasm: Marketing and selling high-tech products to mainstream customers. New York: PerfectBound; 2001.

239. Bass FM, Krishnan TV, Jain DC. Why the Bass Model fits without decision variables. Mark Sci. 1994 Aug;13(3):203–23.

240. Mankins JC. Technology Readiness Levels. A White Paper [Internet]. Advanced Concepts Office, Office of Space Access and Technology, NASA; 1995. Available from: https://aiaa.kavi.com/apps/group_public/download.php/2212/TRLs_Mankins%20Paper_1995.pdf

241. Center for Devices and Radiological Health. Design control guidance for medical device manufacturers [Internet]. USA: Food and Drug Administration (FDA); 1997 Mar [cited 2020 May 14] p. 53. Available from: https://www.fda.gov/media/116573/download

242. Sculpher MJ, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? Health Econ. 2006 Jul;15(7):677–87.

243. Sculpher M, Drummond M, Buxton M. The iterative use of economic evaluation as part of the process of health technology assessment. J Health Serv Res Policy. 1997 Jan;2(1):26–30.

244. Sheredos SJ, Cupo ME. The Department of Veterans Affairs Rehabilitation Research and Development Service's Technology Transfer Process. Technol Disabil. 1997;7(1–2):25–9.

245. Feigal DW. Appendix D Impact of the regulatory framework on medical device development and innovation. In: Wizemann T, editor. Public Health Effectiveness of the FDA 510(k) Clearance Process: Balancing Patient Safety and Innovation: Workshop Report [Internet]. Washington (DC): National Academies Press (US); 2010 [cited 2020 Jan 20]. p. 113–28. Available from: http://www.ncbi.nlm.nih.gov/books/NBK209791/

246. Strategic Plan - Total Product Life Cycle Model [Internet]. [cited 2021 May 25]. Available from: https://webarchive.library.unt.edu/eot2008/20081023160331/http://www.fda.gov/cdrh/strategic/tplc.html

247. Hausman ED, Altaie SS. Regulatory aspects of total product life cycle. Diabetes Technol Ther. 2004 Dec;6(6):761–6.

248. Glasgow RE, Vogt T, Boles S. Evaluating the public health impact of health promotion interventions: The RE-AIM framework. Am J Public Health. 1999 Sep;89(9):1322–7.

249. Cheng M. A guide for the development of medical device regulations [Internet]. Estados Unidos: Pan American Health Organization; 2002. 66 p. Available from: https://www.paho.org/hq/dmdocuments/2009/AguideforthedevelopmentofMedicalDevicesRegulations.pdf

250. Clarkson PJ, Buckle P, Coleman R, Stubbs D, Ward J, Jarrett J, et al. Design for patient safety: A review of the effectiveness of design in the UK health service. J Eng Des. 2004 Apr;15(2):123–40.

251. Greenhalgh T, Robert G, Macfarlane F, Bate P, Kyriakidou O. Diffusion of innovations in service organizations: Systematic review and recommendations. Milbank Q. 2004;82(4):581–629.

252. Meade PT, Rabelo L. The technology adoption life cycle attractor: Understanding the dynamics of high-tech markets. Technol Forecast Soc Change. 2004 Sep;71(7):667–84.

253. Temple-Bird C, Kawohl W, Lenel A, Kaur M. How to plan and budget for your healthcare technology. St. Albans: Teaching-aids At Low Cost; 2006. 299 p. ('How to Manage' Series for Healthcare Technology).

254. Mankins JC. Technology readiness and risk assessments: A new approach. Acta Astronaut. 2009 Nov;65(9–10):1208–15.

255. Ergina PL, Cook JA, Blazeby JM, Boutron I, Clavien PA, Reeves BC, et al. Challenges in evaluating surgical innovation. Lancet. 2009 Sep 26;374(9695):1097–104.

256. Barkun JS, Aronson JK, Feldman LS, Maddern GJ, Strasberg SM. Evaluation and stages of surgical innovations. Lancet. 2009 Sep 26;374(9695):1089–96.

257. McCulloch P, Hirst, Maruthappu M. A plan for whole-life-cycle scientific evaluation of surgical innovation: The Idea, Development, Exploration, Assessment, Long-term study (IDEAL) recommendations. J Am Coll Surg. 2014;219(4):e160.

258. Phaal R, O'Sullivan E, Routley M, Ford S, Probert D. A framework for mapping industrial emergence. Technol Forecast Soc Change. 2011 Feb;78(2):217–30.

259. Phaal R, O'Sullivan E, Farrukh C, Probert D. Developing a framework for mapping industrial emergence. In: PICMET '09 - 2009 Portland International Conference on Management of Engineering Technology. 2009. p. 428–40.

260. Croslin D. Innovate the future: A radical new approach to IT innovation. Prentice Hall; 2010. 281 p.

261. Neugebauer EAM, Becker M, Buess GF, Cuschieri A, Dauben HP, Fingerhut A, et al. EAES recommendations on methodology of innovation management in endoscopic surgery. Surg Endosc. 2010 Jul;24(7):1594–615.

262. Bhuiyan N. A framework for successful new product development. J Ind Eng Manag. 2011 Dec 11;4(4):746–70.

263. Rasmussen E. Understanding academic entrepreneurship: Exploring the emergence of university spin-off ventures using process theories. Int Small Bus J. 2011 Oct 1;29(5):448–71.

264. Therapeutic Goods Administration. Therapeutic product vigilance [Internet]. Australia: Therapeutic Goods Administration, Department of Health; 2017 p. 15. Report No.: v1.4 September 2017. Available from: https://www.tga.gov.au/publication/therapeutic-product-vigilance

265. Health Canada. Health product vigilance framework. [Internet]. Ottawa, Ontario: Health Canada; 2013 [cited 2019 Oct 14]. Available from: http://ra.ocls.ca/ra/login.aspx?inst=centennial&url=https://www.deslibris.ca/ID/235384

266. Extension and Outreach, College of Engineering. CIRAS innovation cycle brochure [Internet]. Iowa State University; 2013. Available from: www.ciras.iastate.edu

267. Wright JG, Weinstein S. The Innovation Cycle: A framework for taking surgical innovation into clinical practice. J Bone Jt Surg. 2013 Nov 6;95(21):e164.

268. NASA Office of the Chief Engineer (OCE). NASA Systems Engineering Handbook [Internet]. Rev 2. Washington, D.C: National Aeronautics and Space Administration (NASA); 2016 [cited 2018 Nov 26]. 356 p. Available from: https://ntrs.nasa.gov/archive/nasa/casi.ntrs.nasa.gov/20170001761.pdf

269. Pecoraro F, Luzi D. The integration of the risk management process with the lifecycle of medical device software. Methods Inf Med. 2014;53(2):92–8.

270. Provoost V, Tilleman K, D'Angelo A, De Sutter P, de Wert G, Nelen W, et al. Beyond the dichotomy: A tool for distinguishing between experimental, innovative and established treatment. Hum Reprod. 2014 Mar;29(3):413–7.

271. Reeves O, Garcia J. Life cycle of medical devices: Lifecycle approach to regulation & the importance of reporting incidents to the TGA [Internet]. Conference presentation presented at: Australian Biomedical Engineering Conference; 2014 Aug 20; National Convention Centre Canberra. Available from: https://www.tga.gov.au/presentation-life-cycle-medical-devices

272. Baeyens A. How the new Procurement Directive may contribute to spur innovative purchases in the health sector. Launch of the IMDA Strategy 2016-2020 Dublin; 2016 Feb 11; Royal College of Physicians, 6 Kildare Street, Dublin 2.

273. Pennell CP, Hirst AD, Campbell WB, Sood A, Agha RA, Barkun JST, et al. Practical guide to the Idea, Development and Exploration stages of the IDEAL Framework and Recommendations. Br J Surg. 2016 Apr;103(5):607–15.

274. Greenhalgh T, Wherton J, Papoutsi C, Lynch J, Hughes G, A'Court C, et al. Beyond adoption: A new framework for theorizing and evaluating nonadoption, abandonment, and challenges to the scale-up, spread, and sustainability of health and care technologies. J Med Internet Res. 2017 01;19(11):e367.

275. Gutiérrez-Ibarluzea I, Chiumente M, Dauben HP. The life cycle of health technologies. Challenges and ways forward. Front Pharmacol. 2017 Jan 24;8(Article 14):1–4.

276. Hannan R, Arora V, Beaver R, Harvie P. How should new orthopaedic implants be introduced: An example and recommendations for best practice. ANZ J Surg. 2017 Nov 9;88(4):284–9.

277. OECD. New health technologies: Managing access, value and sustainability [Internet]. Paris: OECD Publishing; 2017 [cited 2018 Aug 8]. 228 p. Available from: http://www.oecd-ilibrary.org/social-issues-migration-health/new-health-technologies/new-health-technologies-managing-access-value-and-sustainability_9789264266438-4-en

278. Swissmedic 2017 © Copyright. Guide to the regulation of medical devices [Internet]. 2017 [cited 2018 Jul 16]. Available from: https://www.swissmedic.ch/swissmedic/en/home/medical-devices/regulation-of-medical-devices/medical-device-regulation_online-guide.html

279. Office of the Commissioner. The Device Development Process [Internet]. FDA. FDA; 2020 [cited 2021 Apr 28]. Available from: https://www.fda.gov/patients/learn-about-drug-and-device-approvals/device-development-process

280. JA3 Work Package 5 – Lifecycle Approach to improve Evidence Generation – EUnetHTA [Internet]. [cited 2021 May 9]. Available from: https://eunethta.eu/ja3-archive/work-package-5-life-cycle-approach-to-improve-evidence-generation/

281. Bass FM. A new product growth for model consumer durables. Manage Sci. 1969;15(5):215–27.

282. Harkin KR, Sorensen J, Thomas S. Lifecycle evaluation of medical devices: Supporting or jeopardizing patient outcomes? A comparative analysis of evaluation models. International Journal of Technology Assessment in Health Care. 2024 Jan;40(1):e2.

283. Morelli L., Guadagni S., Di Franco G., Palmeri M., Di Candio G., Mosca F. Da Vinci single site© surgical platform in clinical practice: a systematic review. Int J Med Rob Comput Assisted Surg. 2016;12(4):724–34.

284. Khachane A, Philippou Y, Hirst A, McCulloch P. Appraising the uptake and use of the IDEAL Framework and Recommendations: A review of the literature. Int J Surg. 2018 Aug 9;57:84–90.

285. Siontis GCM, Coles B, Häner JD, McGovern L, Bartkowiak J, Coughlan JJ, et al. Quality and transparency of evidence for implantable cardiovascular medical devices assessed by the CORE-MD consortium. Eur Heart J. 2023 Aug 28;ehad567.

286. Paris V, Slawomirski L, Colbert A. Ensuring timely and affordable access to medical devices. In: OECD. New Health Technologies: Managing Access, Value and Sustainability [Internet]. OECD Publishing; 2017 [cited 2020 Jan 24]. p. 117–58. Available from: https://doi.org/10.1787/9789264266438-7-en

287. Feigal D. Total Product Life Cycle [Internet]. Online presented at; 2003 Jan 16 [cited 2021 Jun 1]. Available from: https://webarchive.library.unt.edu/eot2008/20090120125024/http://www.fda.gov/cdrh/strategic/presentations/tplc.ppt

288. IOM (Institute of Medicine). Public Health Effectiveness of the FDA 510(k) Clearance Process: Balancing Patient Safety and Innovation: Workshop Report [Internet]. Washington, DC: The National Academies Press; 2010 [cited 2018 Dec 5] p. 140. Available from: https://www.nap.edu/download/12960

289. Teixeira MB, Bradley R, Teixeira M. Chapter 3. Overview of design controls. In: Design Controls for the Medical Device Industry [Internet]. Baton Rouge, UNITED STATES: Taylor & Francis Group; 2013 [cited 2020 May 13]. p. 9–16. Available from: http://ebookcentral.proquest.com/lib/trinitycollege/detail.action?docID=1407968

290. McCulloch P, Cook JA, Altman DG, Heneghan C, Diener MK, IDEAL Group. IDEAL framework for surgical innovation 1: The idea and development stages. BMJ. 2013 Jun 18;346:f3012.

291. Meyer F, Brühl H, Ormstad SS. Session 3: Taking lifecycle approach to EUnetHTA's work: Current and future collaboration between Early Dialogues and Relative Effectiveness Assessments [Internet]. 2018 EUnetHTA Forum presented at; 2018 May 25 [cited 2018 Oct 22]; Cologne, Germany. Available from: https://eunethta.eu/wp-content/uploads/2018/05/Session-3-Merged-25-May.pptx

292. EUNetHTA 2018 Assembly & Forum Welcome Guide [Internet]. EUNetHTA; 2018 [cited 2018 Jun 20]. Available from: https://eunethta.eu/wp-content/uploads/2018/05/FINALCombined1_Optimize_Optimize.pdf

293. Galbraith M. Patient involvement: The EUnetHTA Early Dialogues perspective [Internet]. Conference presentation presented at: XPatient Congress Barcelona; 2019 Sep 18 [cited 2023 Sep 12]; Barcelona. Available from: https://xpatientbcncongress.com/wp-content/uploads/2019/10/02_20190918_XPatient_mgalbraith.pdf

294. Greenhalgh T, Robert G, Bate P, Kyriakidou O, MacFarlane F, Peacock R. How to Spread Good Ideas: A systematic review of the literature on diffusion, dissemination and sustainability of innovations in health service delivery and organisation. London, England; 2004 Apr p. 427. (Report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R&D (NCCSDO)).

295. Extension and Outreach, College of Engineering. The Innovation Cycle [Internet]. Iowa State University; 2013 [cited 2018 Feb 14]. Available from: www.ciras.iastate.edu

296. Anand R, Graves SE, de Steiger RN, Davidson DC, Ryan P, Miller LN, et al. What is the benefit of introducing new hip and knee prostheses? J Bone Joint Surg Am. 2011 Dec 21;93 Suppl 3:51–4.

297. Baeyens H, DeBacker C, Pouppez C. Towards a guided and phased introduction of high-risk medical devices in Belgium. 2015;91.

298. Poder TG. Using the Health Technology Assessment toolbox to facilitate procurement: The case of Smart Pumps in a Canadian hospital. Int J Technol Assess Health Care. 2017 Jan;33(1):54–62.

299. Kelly J, Fearns N, Heller-Murphy S. Patient views on antimicrobial dressings in chronic wounds. Br J Nurs. 2016 Mar 24;25(6 Suppl):S6–13.

300. Pedersen VH, Dagenais P, Lehoux P. Multi-source synthesis of data to inform health policy. Int J Technol Assess Health Care. 2011 Jul;27(3):238–46.

301. Feigal D. Strategic Plan - Total Product Life Cycle Model (TPLC) [Internet]. 2003 Jan 16 [cited 2021 May 25]; Available online. Available from: https://webarchive.library.unt.edu/eot2008/20081023160331/http://www.fda.gov/cdrh/strategic/tplc.html

302. Rathi VK, Ross JS, Samuel AM, Mehra S. Postmarket modifications of high-risk therapeutic devices in otolaryngology cleared by the US Food and Drug Administration. Otolaryngol Head Neck Surg. 2015 Sep;153(3):400–8.

303. Barker J.P., Simon S.D., Dubin J. The methodology of clinical studies used by the FDA for approval of high-risk orthopaedic devices. J Bone Jt Surg Am Vol. 2017 May 3;99(9):711–9.

304. Darrow JJ, Avorn J, Kesselheim AS. FDA Regulation and approval of medical devices: 1976-2020. JAMA. 2021 Aug 3;326(5):420–32.

305. Johnston JL, Dhruva SS, Ross JS, Rathi VK. Assessment of FDA approval for new high-risk therapeutic devices not meeting pivotal study primary end points, 2016-2020. JAMA Intern Med. 2021 Jun 21;181(10):1409–12.

306. Rathi VK, Wang B, Ross JS, Downing NS, Kesselheim AS, Gray ST. Clinical evidence supporting US Food and Drug Administration Premarket Approval of high-risk otolaryngologic devices, 2000-2014. Otolaryngol Head Neck Surg. 2017 Feb;156(2):285–8.

307. Zheng SY, Dhruva SS, Redberg RF. Characteristics of clinical studies used for US Food and Drug Administration approval of high-risk medical device supplements. JAMA. 2017 Aug 15;318(7):619–25.

308. McGlinch P, Hutt PB. Hollow government: Resource constraints and workload expansion at the Food and Drug Administration [redacted version] [Internet]. Harvard Law School Library; 2001 [cited 2021 Jun 16]. Available from: https://dash.harvard.edu/bitstream/handle/1/8944673/McGlinch01_redacted.html?sequence=2

309. Herder M. Pharmaceutical drugs of uncertain value, lifecycle regulation at the US Food and Drug Administration, and institutional incumbency. Milbank Q. 2019;97(3):820–57.

310. Heneghan CJ, Goldacre B, Onakpoya I, Aronson JK, Jefferson T, Pluddemann A, et al. Trials of transvaginal mesh devices for pelvic organ prolapse: A systematic database review of the US FDA approval process. BMJ Open. 2017 Dec 6;7(12):e017125.

311. Wizemann T, editor. Public health effectiveness of the FDA 510(k) clearance process: Balancing patient safety and innovation: Workshop report [Internet]. Washington, DC: The National Academies Press: IOM (Institute of Medicine); 2010 [cited 2018 Dec 5]. 140 p. Available from: https://www.nap.edu/read/12960/chapter/11

312. Center for Devices and Radiological Health. Premarket Notification 510(k) [Internet]. FDA. FDA; 2022 [cited 2023 Jan 16]. Available from: https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-notification-510k

313. Nezhat C, Kho K. Iatrogenic myomas: New class of myomas? Journal of Minimally Invasive Gynecology. 2010 Sep 1;17(5):544–50.

314. Noorchashm H, Reed AJ. Tragedy, trade-offs, and the demise of morcellation. New England Journal of Medicine. 2016 Jun 30;374(26):2605–2605.

315. Rathi VK, Krumholz HM, Masoudi FA, Ross JS. Postmarket clinical evidence for high-risk therapeutic medical devices receiving Food and Drug Administration Premarket Approval in 2010 and 2011. JAMA Netw Open. 2020 Aug 3;3(8):e2014496.

316. Cipriani A, Ioannidis JPA, Rothwell PM, Glasziou P, Li T, Hernandez AF, et al. Generating comparative evidence on new drugs and devices after approval. Lancet. 2020 21;395(10228):998–1010.

317. National Competent Authority Report Working Group. Medical devices: Post-market surveillance: National Competent Authority Report exchange criteria and report form. IMDRF/NCAR WG/N14FINAL:2017 (Edition 2) [Internet]. International Medical Device Regulators Forum; 2017 [cited 2020 Feb 16]. Available from: https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-170921-pms-ncar-n14-r2.pdf

318. Kadakia KT, Dhruva SS, Caraballo C, Ross JS, Krumholz HM. Use of recalled devices in new device authorizations under the US Food and Drug Administration's 510(k) pathway and risk of subsequent recalls. JAMA. 2023 Jan 10;329(2):136–43.

319. Zhu A, Ying X, Pean CA, Sheth NP, Cross MB, Gonzalez Della Valle A, et al. The complex process of using the interconnected knee arthroplasty device clearance pathway. HSS J. 2022 Nov;18(4):462–8.

320. Premkumar A, Zhu A, Ying X, Pean CA, Sheth NP, Cross MB, et al. The interconnected ancestral network of hip arthroplasty device approval. J Am Acad Orthop Surg. 2021 Dec 15;29(4):e1362–9.

321. White SK, Walters AN. Assessing risk by analogy: A case study of us medical device risk management policy. Health Risk Soc. 2018 Nov 17;20(7–8):358–78.

322. Naci H, Salcher-Konrad M, Kesselheim AS, Wieseler B, Rochaix L, Redberg RF, et al. Generating comparative evidence on new drugs and devices before approval. Lancet. 2020 Mar 21;395(10228):986–97.

323. Unsafe and ineffective devices approved in the EU that were not approved in the US [Internet]. USA: US Department of Health and Human Services. US Food and Drug Administration; 2012 May [cited 2019 Mar 6] p. 16. Available from: http://www.rai.it/dl/docs/154334136138105-reportFDA.pdf

324. Jiang R. Introduction to Quality and Reliability Engineering. Beijing : Heidelberg: Science Press ; Springer; 2015. 336 p. (Springer Series in Reliability Engineering).

325. Wynn DC, Clarkson PJ. Process models in design and development. Res Eng Design. 2018 Apr 1;29(2):161–202.

326. Alexander K, Clarkson J, Bishop D, Fox S. Good design practice for medical devices and equipment - a framework. Cambridge: University of Cambridge Engineering Design Centre : Cambridge Consultants; 2001. 64 p.

327. Shefelbine S, Clarkson J, Famer R, Eason S. Good design practice for medical devices and equipment - requirements capture. Cambridge: Cambridge Engineering Design Centre; 2002. 80 p.

328. CFR - Code of Federal Regulations Title 21 [Internet]. [cited 2021 Mar 22]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=820&showFR=1

329. Crawford GA, Revised by: Howard Stanley. 2-20-2019. The Design Process: Embodiment Design and Detail Design [Internet]. 2017 Mar 22 [cited 2021 Feb 9]. Available from: http://showard.sdsmt.edu/MET352/05_Power%20Point%20Slides/Design%20Process%20-%20Embodiment%20Design%20and%20Detail%20Design_rev2_MET%20352%20Spring%202019.pdf

330. Clinical Applications of Biomaterials. NIH Consens Statement Online. 1982 Nov 1-3; 4(5):1-19 [Internet]. [cited 2021 Mar 24]. Available from: https://consensus.nih.gov/1982/1982Biomaterials034html.htm

331. Williams DF. On the mechanisms of biocompatibility. Biomaterials. 2008 Jul;29(20):2941–53.

332. Williams DF. There is no such thing as a biocompatible material. Biomaterials. 2014 Dec;35(38):10009–14.

333. Pandit A. Concepts of Biocompatibility [Internet]. Fundamentals in Medical Device Design and Regulation; 2019 Nov [cited 2021 Mar 24]; Online CRDI Course. Available from: https://crdi.ie/education/courses/online-crdi-course-fundamentals-medical-device-design-regulation-gen/

334. Zeugolis DI. A Biomaterials Design Perspective [Internet]. Fundamentals in Medical Device Design and Regulation; 2019 Nov [cited 2021 Mar 24]; Online CRDI Course. Available from: https://crdi.ie/education/courses/online-crdi-course-fundamentals-medical-device-design-regulation-gen/

335. Booker J, Raines M, Swift K. 1. Introduction to quality and reliability engineering. In: Designing capable and reliable products. Berlin Heidelberg: Springer-Verlag; 2001. p. 1–36.

336. Booker J, Raines M, Swift K. Appendix III: Overview of the key tools and techniques. In: Designing capable and reliable products. Berlin Heidelberg: Springer-Verlag; 2001. p. 1–36.

337. Booker J, Raines M, Swift K. 3. Designing capable assembly stacks. In: Designing capable and reliable products. Berlin Heidelberg: Springer-Verlag; 2001. p. 1–36.

338. Ward J, Clarkson J, Bishop D, Fox S. Good design practice for medical devices and equipment - design verification. Cambridge: University of Cambridge Engineering Design Centre : Cambridge Consultants; 2002. 80 p.

339. Sheremetiev D. Guide for Industrial Designers starting in Medical Device Development. 2019 Mar; National College of Art and Design (NCAD), Dublin.

340. International Organization for Standardization (ISO). ISO 13485 Quality management for medical devices [Internet]. International Organization for Standardization (ISO); 2016 [cited 2019 Mar 23]. Available from: https://www.iso.org/files/live/sites/isoorg/files/store/en/PUB100377.pdf

341. International Organization for Standardization (ISO). Online Browsing Platform (OBP) Terms & Definitions [Internet]. International Organization for Standardization (ISO) Online Browsing Platform (OBP). [cited 2021 Mar 29]. Available from: https://www.iso.org/obp/ui#search

342. National Standards Authority of Ireland (NSAI). I.S. EN ISO 14791:2019. Medical devices - Application of risk management to medical devices. Dublin: NSAI; 2019. 58 p.

343. Stuart M. Course Manual: PG Certificate in Statistics, TCD. Design and Analysis of Experiments Module: Chapter 1. 2018.

344. WTO | The WTO in brief [Internet]. [cited 2023 Apr 3]. Available from: https://www.wto.org/english/thewto_e/whatis_e/inbrief_e/inbr_e.htm

345. WTO | What is the WTO? - About the WTO – A statement by former Director-General Pascal Lamy [Internet]. [cited 2023 Apr 3]. Available from: https://www.wto.org/english/thewto_e/whatis_e/wto_dg_stat_e.htm

346. Santana R. 70th anniversary of the GATT: Stalin, the Marshall Plan, and the provisional application of the GATT 1947. Trade Law & Development. 2017;9(2):118–37.

347. WTO | The history of multilateral trading system [Internet]. [cited 2023 Apr 3]. Available from: https://www.wto.org/english/thewto_e/history_e/tradewardarkhour41_e.htm

348. From GATT to WTO [Internet]. 2022 [cited 2023 Apr 3]. Available from: https://www.youtube.com/watch?v=rdX3xPSywgU

349. WTO | legal texts - Revised Agreement on Government Procurement [Internet]. [cited 2023 Apr 3]. Available from: https://www.wto.org/english/docs_e/legal_e/rev-gpr-94_01_e.htm

350. World Health Organization. History [Internet]. About WHO. 2023 [cited 2023 Apr 3]. Available from: https://www.who.int/about/history

351. World Health Organization. Who we are [Internet]. 2023 [cited 2023 Apr 3]. Available from: https://www.who.int/about/who-we-are

352. World Health Organization (WHO). Medical devices [Internet]. [cited 2021 Apr 9]. Available from: https://www.who.int/westernpacific/health-topics/medical-devices

353. World Health Organization. Human resources for medical devices, the role of biomedical engineers [Internet]. Geneva: World Health Organization; 2017 [cited 2022 Dec 31]. 240 p. (WHO Medical device technical series). Available from: https://apps.who.int/iris/handle/10665/255261

354. World Health Organization. Introduction to medical equipment inventory management [Internet]. Geneva, Switzerland: World Health Organization; 2011 [cited 2022 Dec 31]. 30 p. (WHO Medical device technical series). Available from: https://apps.who.int/iris/handle/10665/44561

355. World Health Organization. Computerized maintenance management system [Internet]. Geneva, Switzerland: World Health Organization; 2011 [cited 2022 Dec 31]. 41 p. (WHO Medical device technical series). Available from: https://apps.who.int/iris/handle/10665/44567

356. World Health Organization. Decommissioning medical devices [Internet]. Geneva: World Health Organization; 2019 [cited 2022 Dec 31]. 52 p. (WHO Medical device technical series). Available from: https://apps.who.int/iris/handle/10665/330095

357. World Health Organization. Management and Use [Internet]. World Health Organization | Health products policy and standards. 2023 [cited 2023 Apr 3]. Available from: https://www.who.int/teams/health-product-policy-and-standards/assistive-and-medical-technology/medical-devices/management-use

358. Who We Are - PAHO/WHO | Pan American Health Organization [Internet]. [cited 2023 Aug 8]. Available from: https://www.paho.org/en/who-we-are

359. Eccleston RC. A model regulatory program for medical devices an international guide. Washington: PAHO; 2001. 72 p.

360. GHTF. Notes from the SG 1 meeting of 23 – 25 March 1999 in Brussels [Internet]. Global Harmonization Task Force (GHTF); 1999 [cited 2023 Mar 30]. Available from: https://www.imdrf.org/sites/default/files/docs/ghtf/final/sg1/meetings/ghtf-sg1-meeting-minutes-990323-belgium-brussels.pdf

361. GHTF History [Internet]. [cited 2020 Feb 22]. Available from: http://www.imdrf.org/ghtf/ghtf-history.asp

362. Davies C. GHTF Minutes - Steering Committee - 1st Meeting [Internet]. Global Harmonization Task Force (GHTF); 2001 [cited 2022 Jan 14]. Available from: https://www.imdrf.org/sites/default/files/docs/ghtf/final/steering-committee/meetings/ghtf-sc-meeting-minutes-010228-sydney-australia.pdf

363. Carvalho A. GHTF Guiding Principles [Internet]. Global Harmonization Task Force (GHTF); 2005 [cited 2020 Sep 28] p. 7. Report No.: GHTF/SC/N1R8:2005. Available from: https://www.imdrf.org/sites/default/files/2022-05/ghtf-sc-n1r8-050520-ghtf-guiding-principles.pdf

364. Ad Hoc GHTF SC Regulatory Model Working Group. The GHTF Regulatory Model [Internet]. Global Harmonization Task Force (GHTF); 2011 Apr [cited 2020 Sep 28] p. 27. Report No.: GHTF/AHWG-GRM/N1R13:2011. Available from: https://www.imdrf.org/sites/default/files/docs/ghtf/final/steering-committee/technical-docs/ghtf-sc-n1r13-2011-ad-hoc-regulatory-model-110413.pdf

365. imdrf-meet-120228-singapore-outcome-statement.pdf [Internet]. [cited 2023 Jul 14]. Available from: https://www.imdrf.org/sites/default/files/docs/imdrf/final/meetings/imdrf-meet-120228-singapore-outcome-statement.pdf

366. Working Groups [Internet]. International Medical Device Regulators Forum. [cited 2023 Aug 20]. Available from: https://www.imdrf.org/about/working-groups

367. Spanou D. IMDRF Terms of Reference IMDRF Management Committee International Medical Device Regulators Forum 1 August 2013.

368. IMDRF Terms of Reference_2023 (N1 ToR).pdf [Internet]. [cited 2023 Jul 14]. Available from: https://www.imdrf.org/sites/default/files/2023-02/IMDRF%20Terms%20of%20Reference_2023%20%28N1%20ToR%29.pdf

369. Closed working groups [Internet]. International Medical Device Regulators Forum. [cited 2023 Jul 14]. Available from: https://www.imdrf.org/working-groups/closed-working-groups

370. Working groups [Internet]. International Medical Device Regulators Forum. [cited 2023 Jul 14]. Available from: https://www.imdrf.org/working-groups

371. Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EEC as regards medical devices incorporating stable derivates of human blood or human plasma. OJ L 313, 13.12.2000 Dec 13, 2000 p. 22–4.

372. Directive 2001/104/EC of the European Parliament and of the Council of 7 December 2001 amending Council Directive 93/42/EEC concerning medical devices (Text with EEA relevance). OJ L 6, 10.1.2002 Jan 10, 2002 p. 50–1.

373. Regulation (EC) No 1882/2003 of the European Parliament and of the Council of 29 September 2003 adapting to Council Decision 1999/468/EC the provisions relating to committees which assist the Commission in the exercise of its implementing powers laid down in instruments subject to the procedure referred to in Article 251 of the EC Treaty [Internet]. OJ L, 32003R1882 Oct 31, 2003. Available from: http://data.europa.eu/eli/reg/2003/1882/oj/eng

374. Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market (Text with EEA relevance). OJ L 247, 21.9.2007 Sep 21, 2007 p. 21–55.

375. Hug KT, Watters TS, Vail TP, Bolognesi MP. The withdrawn ASR™ THA and Hip Resurfacing systems: How have our patients fared over 1 to 6 years? Clin Orthop Relat Res. 2013 Feb;471(2):430–8.

376. Cohen D. The truth behind ‘made in Europe’ labels on medical devices. BMJ. 2012 Oct 24;345:e7193.

377. Regulation (EU) 2020/561 of the European Parliament and of the Council of 23 April 2020 amending Regulation (EU) 2017/745 on medical devices, as regards the dates of application of certain of its provisions (Text with EEA relevance). OJ L 130, 24.4.2020 Apr 23, 2020 p. 18–22.

378. Regulation (EU) 2023/607 of the European Parliament and of the Council of 15 March 2023 amending Regulations (EU) 2017/745 and (EU) 2017/746 as regards the transitional provisions for certain medical devices and in vitro diagnostic medical devices (Text with EEA relevance). OJ L 80, 20.3.2023 Mar 15, 2023 p. 24–9.

379. Single European Act [Internet]. OJ L 169 , 29.06.1987 Feb 17, 1986 p. 1–28. Available from: http://data.europa.eu/eli/treaty/sea/sign/eng

380. Office for Official Publications of the European Communities. European Communities - Economic and Social Committee Annual Report 1992. Luxembourg: Economic and Social Committee; 1993 p. 136.

381. Single European Act [Internet]. Single European Act. [cited 2020 Oct 14]. Available from: /about-parliament/en/in-the-past/the-parliament-and-the-treaties/single-european-act

382. Treaty of Lisbon amending the Treaty on European Union and the Treaty establishing the European Community, signed at Lisbon, 13 December 2007 [Internet]. OJ C 306, 17.12.2007., 12007L Dec 13, 2007 p. 1–271. Available from: http://data.europa.eu/eli/treaty/lis/sign/eng

383. Council Resolution of 7 May 1985 on a new approach to technical harmonisation and standards. OJ C 136, 4.6.1985 Jun 4, 1985 p. 1–9.

384. Opinion of the Economic and Social Committee on the proposal for a Council Directive concerning Medical Devices. OJ C 79, 30.3.1992 1992 p. 1–3.

385. Re-examined proposal for a Council Directive relating to medical devices [Internet]. COM(93) 241 final 1993 p. 1–4. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A51993PC0241

386. Treaty on the Functioning of the European Union [Internet]. Dec 13, 2007 p. 344. Available from: https://eur-lex.europa.eu/resource.html?uri=cellar:2bf140bf-a3f8-4ab2-b506-fd71826e6da6.0023.02/DOC_2&format=PDF

387. General Secretariat of the Council (Council of the European Union). Guide to the ordinary legislative procedure [Internet]. Luxembourg: Publications Office of the European Union; 2016 [cited 2020 Jun 29]. Available from: https://data.europa.eu/doi/10.2860/94660

388. Commission Implementing Regulation (EU) No 920/2013 of 24 September 2013 on the designation and the supervision of notified bodies under Council Directive 90/385/EEC on active implantable medical devices and Council Directive 93/42/EEC on medical devices Text with EEA relevance. OJ L 253, 25.9.2013 Sep 24, 2013 p. 8–19.

389. Commission Implementing Decision (EU) 2021/611 of 14 April 2021 amending Implementing Decision (EU) 2020/438 as regards harmonised standards on biological evaluation of medical devices, packaging for terminally sterilised medical devices, sterilisation of health care products and clinical investigation of medical devices for human subjects. OJ L 129, 15.4.2021 Apr 14, 2021 p. 158–60.

390. Commission Implementing Decision (EU) 2020/437 of 24 March 2020 on the harmonised standards for medical devices drafted in support of Council Directive 93/42/EEC, as amended [Internet]. OJ L 90 I, 25.3.2020 Apr 15, 2021 p. 1–28. Available from: http://data.europa.eu/eli/dec_impl/2020/437/2021-04-15/eng

391. Cohen D. Patient groups accuse European parliament of putting economic interests ahead of safety on medical devices. BMJ. 2013 Oct 24;347:f6446.

392. Cohen D. Devices and desires: Industry fights toughening of medical device regulation in Europe. BMJ. 2013 Oct 16;347:f6204.

393. European Commission, Directorate-General III (Industry). Guide to the implementation of directives based on New Approach and Global Approach [Internet]. European Commission; 2000 [cited 2021 Feb 13]. Available from: https://www.walaw.com/bluebook.pdf

394. OJEC C 76, 17.6.1969 [Internet]. [cited 2020 Nov 23]. Available from: https://eur-lex.europa.eu/legal-content/FR/TXT/PDF/?uri=OJ:C:1969:076:FULL&from=FR

395. Commission of the European Communities. Technical harmonization and standards: A new approach. Communication from the Commission to the Council and to the European Parliament on 31 January 1985 [Internet]. European Commission; 1985 [cited 2020 Nov 26]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:51985DC0019&qid=1693345326692

396. Publications Office of the European Union. CELEX1, Council Resolution of 7 May 1985 on a new approach to technical harmonization and standards [Internet]. Publications Office of the European Union; 1985 [cited 2020 May 9]. Available from: http://op.europa.eu/en/publication-detail/-/publication/9f7c3a42-449e-4ccc-9a29-5a544003b338/language-en

397. COUNCIL DIRECTIVE 93/68/EEC [Internet]. [cited 2020 May 9]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31993L0068&from=EN

398. Council Resolution of 21 December 1989 on a global approach to conformity assessment. OJ C 10, 16.1.1990 Dec 21, 1989 p. 1–2.

399. Council Decision of 13 December 1990 concerning the modules for the various phases of the conformity assesment procedures which are intended to be used in the technical harmonization directives (90/683/EEC). OJ L 380, 31.12.1990 Dec 13, 1990 p. 13–26.

400. Council Decision of 22 July 1993 concerning the modules for the various phases of the conformity assessment procedures and the rules for the affixing and use of the CE conformity marking, which are intended to be used in the technical harmonization directives. OJ L 220, 30.8.1993 Jul 22, 1993 p. 23–39.

401. NBOG_BPG_2010_3.pdf [Internet]. [cited 2020 Feb 14]. Available from: http://www.doks.nbog.eu/Doks/NBOG_BPG_2010_3.pdf

402. Directorate-General for Enterprise and Industry (European Commission). Guide to the implementation of directives based on the new approach and the global approach [Internet]. European Commission GROW; 2000. Available from: https://op.europa.eu/en/publication-detail/-/publication/4f6721ee-8008-4fd7-acf7-9d03448d49e5/language-en

403. Council Directive 64/432/EEC of 26 June 1964 on animal health problems affecting intra-Community trade in bovine animals and swine. OJ L 121, 1977, 29.7.64 Jul 29, 1964 p. 164–84.

404. Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products. OJ L 22, 9.2.65 Feb 9, 1965 p. 20–4.

405. Council Directive 73/23/EEC of 19 February 1973 on the harmonization of the laws of Member States relating to electrical equipment designed for use within certain voltage limits. OJ L 77, 26.3.73 Feb 19, 1973 p. 29–33.

406. Decision No 768/2008/EC of the European Parliament and of the Council of 9 July 2008 on a common framework for the marketing of products, and repealing Council Decision 93/465/EEC (Text with EEA relevance). OJ L 218, 13.8.2008 Jul 9, 2008 p. 82–128.

407. Regulation (EC) No 765/2008 of the European Parliament and of the Council of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products and repealing Regulation (EEC) No 339/93 (Text with EEA relevance). OJ L 218, 13.8.2008 Jul 9, 2008 p. 30–47.

408. Regulation (EC) No 764/2008 of the European Parliament and of the Council of 9 July 2008 laying down procedures relating to the application of certain national technical rules to products lawfully marketed in another Member State and repealing Decision No 3052/95/EC (Text with EEA relevance). OJ L 218, 13.8.2008 Jul 9, 2008 p. 21–9.

409. Treaty establishing the European Community (Consolidated version 2002) [Internet]. OJ C 325, 24.12.2002., 12002E Dec 24, 2002 p. 33–184. Available from: http://data.europa.eu/eli/treaty/tec_2002/oj/eng

410. New legislative framework [Internet]. Internal Market, Industry, Entrepreneurship and SMEs - European Commission. 2016 [cited 2020 Oct 17]. Available from: https://ec.europa.eu/growth/single-market/goods/new-legislative-framework_en

411. Transparency register: who is lobbying the EU? (infographic) | News | European Parliament [Internet]. 2018 [cited 2020 Sep 21]. Available from: https://www.europarl.europa.eu/news/en/headlines/eu-affairs/20180108STO91215/transparency-register-who-is-lobbying-the-eu-infographic

412. MedTech Europe. The European medical technology industry in figures 2022 [Internet]. MedTech Europe; 2022 [cited 2023 May 24]. Available from: https://www.medtecheurope.org/wp-content/uploads/2022/09/the-european-medical-technology-industry-in-figures-2022.pdf

413. Altenstetter C. Medical Devices. 1 edition. Routledge; 2017. 304 p.

414. Ex-ministers to face trial in French ‘blood scandal’. BMJ. 1998 Aug 1;317(7154):302–302.

415. Illman J. Richard Lacey: microbiologist who came under fire for claiming a link between mad cow disease and variant CJD in humans. BMJ. 2019;364:l1078.

416. European Commission. PIP Action Plan [Internet]. Internal Market, Industry, Entrepreneurship and SMEs - European Commission. 2016 [cited 2020 May 9]. Available from: https://ec.europa.eu/growth/sectors/medical-devices/current-directives/pip-action-plan_en

417. Cohen D. Notified bodies: Are they fit for purpose? BMJ. 2012 Oct 24;345:e7177.

418. Cohen D. UK health secretary promises to tighten regulatory procedures for medical devices. BMJ [Internet]. 2012 Oct 24 [cited 2020 Feb 24];345. Available from: http://www.bmj.com/content/345/bmj.e7192

419. Commission postpones Medical Devices Regulation [Internet]. European Commission - European Commission. [cited 2020 Apr 28]. Available from: https://ec.europa.eu/commission/presscorner/detail/en/IP_20_589

420. Parliament decides to postpone new requirements for medical devices | News | European Parliament [Internet]. 2020 [cited 2020 Apr 28]. Available from:

https://www.europarl.europa.eu/news/en/press-room/20200415IPR77113/parliament-decides-to-postpone-new-requirements-for-medical-devices

421. EUR-Lex - 32020R0561 - EN - EUR-Lex [Internet]. [cited 2020 Nov 4]. Available from: https://eur-lex.europa.eu/eli/reg/2020/561/oj

422. Study Group 1 of the Global Harmonization Task Force. Summary of technical documentation for demonstrating conformity to the essential principles of safety and performance of medical devices (STED) [Internet]. Global Harmonization Task Force (GHTF); 2008 [cited 2021 Apr 6]. Available from: https://www.imdrf.org/sites/default/files/docs/ghtf/archived/SG1/technical-docs/ghtf-sg1-n011-2008-principles-safety-performance-medical-devices-080221.pdf

423. Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 on general product safety (Text with EEA relevance). OJ L 11, 15.1.2002 Jan 15, 2002 p. 4–17.

424. NANDO (New Approach Notified and Designated Organisations) Information System [Internet]. European Commission - Notified bodes Nando. 2017 [cited 2017 Jul 17]. Available from: http://ec.europa.eu/growth/tools-databases/nando/

425. Guide to Vigilance System for Medical Devices [Internet]. [cited 2019 Feb 13]. Available from: http://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/sur-g0002-guide-to-vigilance-system-for-medical-devices-v4.pdf?sfvrsn=8

426. Principles of Conformity Assessment for Medical Devices [Internet]. [cited 2019 Jan 15]. Available from: http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n78-2012-conformity-assessment-medical-devices-121102.pdf

427. AGEPCom. European co-operation for Accreditation [Internet]. European Accreditation. [cited 2019 Feb 1]. Available from: https://european-accreditation.org/

428. Council Directive 83/189/EEC of 28 March 1983 laying down a procedure for the provision of information in the field of technical standards and regulations. OJ L 109, 26.4.83 Mar 28, 1983 p. 8–12.

429. Kmietowicz Z, Cohen D. Device licensing bodies sometimes put business before safety, an investigation finds. BMJ. 2012 Oct 25;345:e7138.

430. CAMD Aims and Objectives [Internet]. CAMD. [cited 2021 Sep 25]. Available from: https://www.camd-europe.eu/camd-aims-and-objectives/

431. Press Release: Medical devices: European Commission calls for immediate actions - tighten controls, increase surveillance, restore confidence [Internet]. European Commission - European Commission. [cited 2024 Apr 17]. Available from: https://ec.europa.eu/commission/presscorner/detail/en/IP_12_119

432. About us - Welcome to Team NB | Team NB [Internet]. [cited 2021 Sep 24]. Available from: https://www.team-nb.org/about-us/

433. Combe A. Criteria for EA and EA MLA Membership [Internet]. European Accreditation. [cited 2024 Apr 17]. Available from: https://european-accreditation.org/ea-members/criteria-for-membership/

434. Regulation (EU) No 1025/2012 of the European Parliament and of the Council of 25 October 2012 on European standardisation, amending Council Directives 89/686/EEC and 93/15/EEC and Directives 94/9/EC, 94/25/EC, 95/16/EC, 97/23/EC, 98/34/EC, 2004/22/EC, 2007/23/EC, 2009/23/EC and 2009/105/EC of the European Parliament and of the Council and repealing Council Decision 87/95/EEC and Decision No 1673/2006/EC

of the European Parliament and of the Council Text with EEA relevance. OJ L 316, 14.11.2012 Oct 25, 2012 p. 12–33.

435. BS EN ISO 14971:2019 Medical devices. Application of risk management to medical devices [Internet]. [cited 2020 Aug 24]. Available from: https://shop.bsigroup.com/ProductDetail?pid=000000000030407615&utm_source=group+landing+page&utm_medium=referral+&utm_campaign=SM-STAN-BEV-HLTH-BSENISO14971-1911

436. I.S. EN ISO 14971:2019 | Medical Devices Risk Management | SAI Global [Internet]. [cited 2020 Aug 23]. Available from: https://shop.standards.ie/en-ie/Standards/I-S-EN-ISO-14971-2019-856997_SAIG_NSAI_NSAI_2798862/

437. Arrêté royal du 18/03/1999 relatif aux dispositifs médicaux [Internet]. 1993. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=NIM:94823

438. European Commission - DG Enterprise and Industry. Medical Devices: Guidance document - Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative [Internet]. European Commission; 2015 [cited 2019 Feb 17]. Available from: https://ec.europa.eu/docsroom/documents/10328/attachments/1/translations/en/renditions/pdf

439. What is a European Standard (EN)? - CEN-CENELEC [Internet]. [cited 2019 Jan 13]. Available from: https://www.cencenelec.eu/standards/DefEN/Pages/default.aspx

440. NSAI Annual Report 2023. NSAI Technical Committees, NSAI/TC 5 - Healthcare standards [Internet]. Dublin, Ireland: National Standards Authority of Ireland (NSAI); 2023 [cited 2024 Apr 25] p. 12. Available from: https://www.nsai.ie/images/uploads/standards/NSAI_TC_05_HCSC_Committee_Annual_Report_2023.pdf

441. Medical equipment, pharmaceuticals and personal care products [Internet]. [cited 2020 Sep 20]. Available from: https://www.cen.eu/work/Sectors/Healthcare/Pages/Medicalequipment.aspx

442. European Commission - DG Internal Market, Industry, Entrepreneurship and SMEs - Consumer, Environmental and Health Technologies - Health technology and Cosmetics. Clinical evaluation: A guide for manufacturers and notified bodies under Directives 93/42/EEC and 90/385/EEC [Internet]. Publications Office of the European Union; 2016 [cited 2020 Feb 12]. Available from: https://ec.europa.eu/docsroom/documents/17522/attachments/1/translations/

443. Medical Device Clinical Evaluation Working Group. Clinical Evaluation [Internet]. International Medical Device Regulators Forum; 2019 [cited 2020 Feb 16]. Available from: https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-191010-mdce-n56.pdf

444. International Medical Device Regulators Forum (IMDRF). Clinical Investigation [Internet]. International Medical Device Regulators Forum (IMDRF); 2019 [cited 2020 Feb 16]. Available from: https://www.imdrf.org/sites/default/files/docs/ghtf/archived/sg5/technical-docs/ghtf-sg5-n3-clinical-investigations-100212.pdf

445. European Commission DG Health and Consumer Affairs. Guidelines on a Medical Devices Vigilance System - MEDDEV 2.12/1 rev.8 [Internet]. European Commission DG SANCO; 2013 [cited 2019 Sep 23]. Available from: https://ec.europa.eu/docsroom/documents/32305/attachments/1/translations/en/renditions/pdf

446. Federal Institute for Drugs and Medical Devices (BfArM). European Market [Internet]. 2020 [cited 2020 Oct 20]. Available from: https://www.dimdi.de/dynamic/en/medical-devices/european-market/

447. Cardoen G. Overview [Internet]. Public Health - European Commission. 2020 [cited 2020 Jul 28]. Available from: https://ec.europa.eu/health/md_eudamed/overview_en

448. European Commission. European Commission 2029-2024 Allocation of portfolios and services [Internet]. 2019 [cited 2020 Oct 20]. Available from: https://ec.europa.eu/commission/sites/beta-political/files/allocation-portfolios-supporting-services_en.pdf

449. Commission Decision of 19 April 2010 on the European Databank on Medical Devices (Eudamed) (notified under document C(2010) 2363) (Text with EEA relevance). OJ L 102, 23.4.2010 Apr 19, 2010 p. 45–8.

450. European Commission. Market surveillance and vigilance [Internet]. Internal Market, Industry, Entrepreneurship and SMEs - European Commission. 2016 [cited 2019 Mar 1]. Available from: https://ec.europa.eu/growth/sectors/medical-devices/current-directives/market-surveillance_en

451. EUDAMED database - EUDAMED [Internet]. [cited 2022 Mar 29]. Available from: https://ec.europa.eu/tools/eudamed/#/screen/home

452. Delaunay C. Registries in orthopaedics. Orthop Traumatol Surg Res. 2015 Feb;101(1 Suppl):S69-75.

453. Lübbeke A, Silman AJ, Barea C, Prieto-Alhambra D, Carr AJ. Mapping existing hip and knee replacement registries in Europe. Health Policy. 2018 May 1;122(5):548–57.

454. Hopper I, Ahern S, Nguyen TQ, Mulvany C, McNeil JJ, Deva AK, et al. Breast implant registries: A call to action. Aesthet Surg J. 2018 Jun 13;38(7):807–10.

455. Daly JO, Ahern S, Herkes R, O'Connell HE. The Australasian Pelvic Floor Procedure Registry: Not before time. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2019;59(4):473–6.

456. Zhang S, Gaiser S, Kolominsky-Rabas PL. Cardiac implant registries 2006–2016: A systematic review and summary of global experiences. BMJ Open. 2018 Apr 12;8(4):e019039.

457. Kynaston-Pearson F, Ashmore AM, Malak TT, Rombach I, Taylor A, Beard D, et al. Primary hip replacement prostheses and their evidence base: Systematic review of literature. Br Med J. 2013 Dec 19;347(dec19 2):f6956–f6956.

458. Graves SE. What is happening with hip replacement? Medical Journal of Australia. 2011;194(12):620–1.

459. ODEP [Internet]. [cited 2018 Nov 29]. Available from: http://www.odep.org.uk/Home.aspx#acceptCookieWarning

460. Erlinge D. Post-market clinical follow-up and registries – the example from SWEDEHEART [Internet]. Conference presented at: European Society of Cardiology (ESC) Meeting: 'Engaging with the new European regulatory landscape for medical devices – Challenges and opportunities'; 2018 Mar 21 [cited 2024 Feb 20]; Brussels, Belgium. Available from: https://www.escardio.org/static-file/Escardio/Advocacy/Documents/David%20Erlinge_Post-market%20clinical%20follow-up%20and%20registries.pdf

461. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, et al. The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). Heart. 2010 Oct 15;96(20):1617–21.

462. Bäck M, Leosdottir M, Hagström E, Norhammar A, Hag E, Jernberg T, et al. The SWEDEHEART secondary prevention and cardiac rehabilitation registry (SWEDEHEART CR registry). Eur Heart J Qual Care Clin Outcomes. 2021 Sep 16;7(5):431–7.

463. UK National Health Service (NHS). Home [Internet]. Scan4Safety. 2024 [cited 2024 Apr 12]. Available from: https://scan4safety.nhs.uk/

464. Study Group 2 of the Global Harmonization Task Force. Global medical devices competent authority report [Internet]. Global Harmonization Task Force; 2003 Jan [cited 2022 Jan 14] p. 6. Report No.: GHTF/SG2/N9R11:2003. Available from: https://www.imdrf.org/sites/default/files/2021-12/ghtf-sg2-n9r11-2003-global-medical-devices-competent-authority-report-030101.pdf

465. Study Group 2 of the Global Harmonization Task Force. Medical Devices: Post Market Surveillance: National Competent Authority Report exchange criteria [Internet]. Global Harmonization Task Force; 2002 May p. 7. Report No.: GHTF/SG2/N20R10:2002. Available from: https://www.imdrf.org/sites/default/files/2021-12/ghtf-sg2-national-competent-authority-report-exhange-criteria-020512.pdf

466. Study Group 2 of the Global Harmonization Task Force. Medical Devices: Post Market Surveillance: National Competent Authority Report exchange criteria and report form [Internet]. Global Harmonization Task Force; 2005 Sep [cited 2020 Feb 16] p. 13. Report No.: SG2(PD)/N79R5. Available from: www.imdrf.org/docs/ghtf/final/sg2/technical-docs/ghtf-sg2-n79r5-ncar-exchange-criteria-report-form-050915.pdf

467. GHTF Study Group 2. Application requirements for participation in the GHTF National Competent Authority Report Exchange Program [Internet]. Global Harmonization Task Force (GHTF); 2009 Jul [cited 2023 Apr 3] p. 9. Report No.: GHTF/SG2/N38R19:2009. Available from: https://www.imdrf.org/sites/default/files/2021-12/ghtf-sg2-n38r19-national-competent-authority-report-program-090701_0.pdf

468. 2007-2010 NCARs Statistics [Internet]. European Commission; [cited 2019 Aug 22] p. 7. Available from: https://ec.europa.eu/docsroom/documents/12980/attachments/5/translations

469. Demade I. Revision of the NCAR Exchange Program [Internet]. IMDRF Sydney; 2012 Sep 23 [cited 2020 Sep 21]; Sydney, Australia. Available from: https://www.imdrf.org/sites/default/files/docs/imdrf/final/work-items/imdrf-wi-120923-presentation-ncar.pdf

470. Bronfenbrenner U. The ecology of human development: Experiments by nature and design. Cambridge, Mass: Harvard University Press; 1979. 330 p.

471. Rosa EM, Tudge J. Urie Bronfenbrenner's Theory of Human Development: Its evolution from ecology to bioecology. Journal of Family Theory & Review. 2013;5(4):243–58.

472. What is Bronfenbrenner's Ecological Systems Theory? [Internet]. The Psychology Notes Headquarters. 2019 [cited 2019 Oct 20]. Available from: https://www.psychologynoteshq.com/bronfenbrenner-ecological-theory/

473. Wren-Lewis L. Chapter 7. Regulatory capture: Risks and solutions. In: Estache A, editor Emerging Issues in Competition, Collusion, and Regulation of Network Industries. London: Centre for Economic Policy Research (CEPR); 2011. p. 147–69.

474. Saltelli A, Dankel DJ, Di Fiore M, Holland N, Pigeon M. Science, the endless frontier of regulatory capture. Futures. 2022 Jan 1;135:102860.

475. Kickbusch I, Allen L, Franz C. The commercial determinants of health. Lancet Glob Health. 2016 Dec 1;4(12):e895–6.

476. Madureira Lima J, Galea S. Corporate practices and health: A framework and mechanisms. Glob Health. 2018 Dec;14(1):21.

477. Mialon M. An overview of the commercial determinants of health. Glob Health. 2020 Dec;16(1):1–7.

478. Goldberg RF, Vandenberg LN. The science of spin: Targeted strategies to manufacture doubt with detrimental effects on environmental and public health. Environ Health. 2021 Dec;20(1):1–11.

479. Reed G, Hendlin Y, Desikan A, MacKinney T, Berman E, Goldman GT. The disinformation playbook: How industry manipulates the science-policy process—and how to restore scientific integrity. J Public Health Pol. 2021 Dec 1;42(4):622–34.

480. Maani N, Schalkwyk MC van, Petticrew M, Buse K. The pollution of health discourse and the need for effective counter-framing. BMJ. 2022 May 4;377:o1128.

481. Michaels D. Doubt is their product: How industry's assault on science threatens your health. Oxford New York, NY: Oxford Univ. Press; 2008. 372 p.

482. Bird T, Steffen JE, Tran TH, Egilman DS. A review of the talc industry's influence on Federal regulation and scientific standards for asbestos in talc. New Solut. 2021 Aug;31(2):152–69.

483. Wilson CB. Adoption of new surgical technology. BMJ. 2006 Jan 14;332(7533):112–4.

484. New EU rules to ensure safety of medical devices [Internet]. [cited 2017 May 22]. Available from: http://ec.europa.eu/DocsRoom/documents/22522

485. Dhruva SS, Ross JS, Desai NR. Real-world evidence: Promise and peril for medical product evaluation. P T. 2018 Aug;43(8):464–72.

486. Tse ACB. Factors affecting consumer perceptions on product safety-The case of nondurables. J Int Consum Mark. 1999 Dec 1;12(1):39–55.

487. Luce BR, Brown RE. The use of technology assessment by hospitals, Health Maintenance Organizations, and third-party payers in the United States. Int J Technol Assess Health Care. 1995 Dec;11(01):79–92.

488. Hulstaert F, Neyt M, Vinck I, Stordeur S, Huić M, Sauerland S, et al. The pre-market clinical evaluation of innovative high-risk medical devices. 2011;46.

489. Gartenberg AJ, Peleg A, Dhruva SS, Redberg RF. Presumed safe no more: Lessons from the Wingspan saga on regulation of devices. BMJ. 2014 Jan 22;348:g93.

490. Dubin JR, Simon SD, Norrell K, Perera J, Gowen J, Cil A. Risk of recall among medical devices undergoing US Food and Drug Administration 510(k) clearance and Premarket Approval, 2008-2017. JAMA Netw Open. 2021 May 3;4(5):e217274.

491. Heilman DK, Jones RT, Swanson MC, Yunginger JW. A prospective, controlled study showing that rubber gloves are the major contributor to latex aeroallergen levels in the operating room. Journal of Allergy and Clinical Immunology. 1996 Aug 1;98(2):325–30.

492. ‘Very concerning’ – Temple Street review as 19 children had complications after spinal surgery in hospital | Independent.ie [Internet]. [cited 2023 Sep 21]. Available from: https://www.independent.ie/irish-news/very-concerning-temple-street-review-as-19-children-had-complications-after-spinal-surgery-in-hospital/a665640495.html

493. Fujita-Rohwerder N, Sauerland S. Bewertung von Medizinprodukten auf europäischer Ebene gemäß der neuen HTA Verordnung (HTAR) – Welche Evidenz erwartet uns? In Potsdam, Germany.;

494. Kisser A, Tüchler H, Erdös J, Wild C. Factors influencing coverage decisions on medical devices: A retrospective analysis of 78 medical device appraisals for the Austrian hospital benefit catalogue 2008-2015. Health Policy. 2016 Aug;120(8):903–12.

495. Campbell B, Knox P. Promise and plausibility: Health technology adoption decisions with limited evidence. Int J Technol Assess Health Care. 2016 Jan;32(3):122–5.

496. Zaletel M, Kralj M, editors. Methodological guidelines and recommendations for efficient and rational governance of patient registries [Internet]. Ljubljana, Slovenia: National Institute of Public Health, Trubarjeva 2, 1000 Ljubljana, Slovenia; 2015 [cited 2018 Apr 26]. 232 p. Available from: https://ec.europa.eu/health/sites/health/files/ehealth/docs/patient_registries_guidelines_en.pdf

497. Lübbeke A, Silman AJ, Prieto-Alhambra D, Adler AI, Barea C, Carr AJ. The role of national registries in improving patient safety for hip and knee replacements. BMC Musculoskelet Disord. 2017 Oct 16;18(1):414.

498. Liu FX, Rutherford P, Smoyer-Tomic K, Prichard S, Laplante S. A global overview of renal registries: A systematic review. BMC Nephrol. 2015 Dec;16(1):31.

499. Mandeville KL, Valentic M, Ivankovic D, Pristas I, Long J, Patrick HE. Quality assurance of registries for Health Technology Assessment. International Journal of Technology Assessment in Health Care. 2018;34(4):360–7.

500. Niederländer CS, Kriza C, Kolominsky-Rabas P. Quality criteria for medical device registries: best practice approaches for improving patient safety - a systematic review of international experiences. Expert Rev Med Devices. 2017 Jan;14(1):49–64.

501. Gliklich RE, Dreyer NA, editors. Registries for evaluating patient outcomes: a user’s guide. Third edition. Rockville, MD: U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality; 2014. 2 p. (AHRQ publication).

502. MedTech Europe, from diagnosis to cure - Homepage [Internet]. MedTech Europe. [cited 2023 Sep 23]. Available from: https://www.medtecheurope.org/

503. European Commission. New EU rules to ensure safety of medical devices [Internet]. European Commission - European Commission. 2017 [cited 2020 Mar 31]. Available from: https://ec.europa.eu/commission/presscorner/detail/en/MEMO_17_848

504. European Commission. Directorate General for Health and Food Safety. Medical Devices - Sector Overview [Internet]. Public Health. 2023 [cited 2023 Jul 21]. Available from: https://health.ec.europa.eu/medical-devices-sector/overview_en

505. The Bleeding Edge: Behind the terrifying new Netflix documentary | Film | The Guardian [Internet]. [cited 2019 Jan 7]. Available from: https://www.theguardian.com/film/2018/jul/25/the-bleeding-edge-netflix-documentary-medical-devices

506. Samaniego Alonso R, Gaviria Parada E, Pons Cabrafiga M, Espallargues Carreras M, Martinez Cruz O. Arthroplasty knee registry of Catalonia: What scientific evidence

supports the implantation of our prosthesis? Rev Esp Cir Ortop Traumatol (Engl Ed). 2018 Feb 28;62(4):290–6.

507. Chaverri-Fierro D, Lobo-Escolar L, Espallargues M, Martinez-Cruz O, Domingo L, Pons-Cabrafiga M. Primary total hip arthroplasty in Catalonia: What is the clinical evidence that supports our prosthesis? Rev Esp Cir Ortop Traumatol. 2016/12/06 ed. 2017 May;61(3):139–45.

508. Oviedo Convention and its Protocols [Internet]. Bioethics. [cited 2021 Sep 26]. Available from: https://www.coe.int/en/web/bioethics/oviedo-convention

509. Tarricone R, Ciani O, Torbica A, Brouwer W, Chaloutsos G, Drummond MF, et al. Lifecycle evidence requirements for high-risk implantable medical devices: A European perspective. Expert Rev Med Devices. 2020;17(10):993–1006.

510. World Health Organization. WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices [Internet]. World Health Organization (WHO). [cited 2018 Jan 22]. Available from: http://www.who.int/medical_devices/publications/global_model_regulatory_framework_meddev/en/

14. Appendices

14.1. Contribution

Publications

1. Hulstaert F, Pouppez C, Primus-de Jong C, Harkin K, Neyt M. Evidence gaps for drugs and medical devices at market entry in Europe and potential solutions [Internet]. BE: KCE = Federaal Kenniscentrum voor de Gezondheidszorg = Centre Fédéral d'Expertise des Soins de Santé = Belgian Health Care Knowledge Centre; 2021 [cited 2023 Dec 13]. 221 p. Available from: https://doi.org/10.57598/R347C
2. Hulstaert F, Pouppez C, Primus-de Jong C, Harkin K, Neyt M. Summary: Evidence gaps for drugs and medical devices at market entry in Europe and potential solutions [Internet]. Brussels: Belgian Health Care Knowledge Centre (KCE); 2021 [cited 2021 Dec 17] p. 46. Report No.: KCE Reports 347Cs. Available from: https://kce.fgov.be/sites/default/files/atoms/files/KCE_347_Evidence_gaps_Europe_Report_V2.pdf
3. Hulstaert F, Pouppez C, Primus-de Jong C, Harkin K, Neyt M. Gaps in the evidence underpinning high-risk medical devices in Europe at market entry, and potential solutions. Orphanet J Rare Dis. 2023 Dec;18(1):1–13.
4. Harkin KR, Sorensen J, Thomas S. Lifecycle evaluation of medical devices: Supporting or jeopardizing patient outcomes? A comparative analysis of evaluation models. Int J Technol Assess Health Care. 2024 Jan;40(1):e2.

Oral and Poster Presentations

- Harkin K, Sorensen J, Thomas S. What does the CE Marking on medical devices mean? Conference poster presented at: SPHeRE Network 10th Annual Conference: Health Services Research: Improving population health and influencing health system reform; 2024 Feb 29; Royal College of Surgeons (RCSI), 123 St Stephen's Green, Dublin 2, Ireland.
- Harkin K, Sorensen J, Thomas S. OP37 Lifecycle evaluation models and frameworks used to assess medical devices: A Qualitative Evidence Synthesis. Int J Technol Assess Health Care. 2022 Dec;38(S1):S15–S15.
- Harkin K, Thomas S, Sorensen J. Who regulates medical devices? A regulatory review [Internet]. Poster presented at: 6th Annual SPHeRE Network Conference 2020; 2020 Feb 25; Royal College of Surgeons (RCSI), 123 St Stephen's Green, Dublin 2, Ireland. Available from: https://drive.google.com/file/d/1cd48e7rnye5eJLHH56UUn2Gnp3BHuLrF/view
- Harkin K, Dee A. OP93 Collaboration between Health Technology Assessment and Procurement: A rapid Mixed-Methods study. Int J Technol Assess Health Care. 2019;35(S1):23–4.
- Harkin K. Regulation of medical devices: What does it mean? Oral Presentation presented at: Irish Society of Community & Public Health Medicine (ISC&PHM) Annual Scientific Meeting; 2019 Oct 25; Westbury Hotel, Dublin.
- Harkin K, Dee A. PP66 Hospital cleaning: Detergent or disinfectant-detergent? A rapid review. Int J Technol Assess Health Care. 2018;34(S1):92–3.

Internal Unpublished Report

- *An exploration of examples of collaboration between HTA and Procurement bodies in the procurement of medical devices: A mixed-methods study*. Report submitted to Dr Anne Dee, HSE Health Technology Assessment Group (HTAG). December 2017.

Awards/Qualifications earned

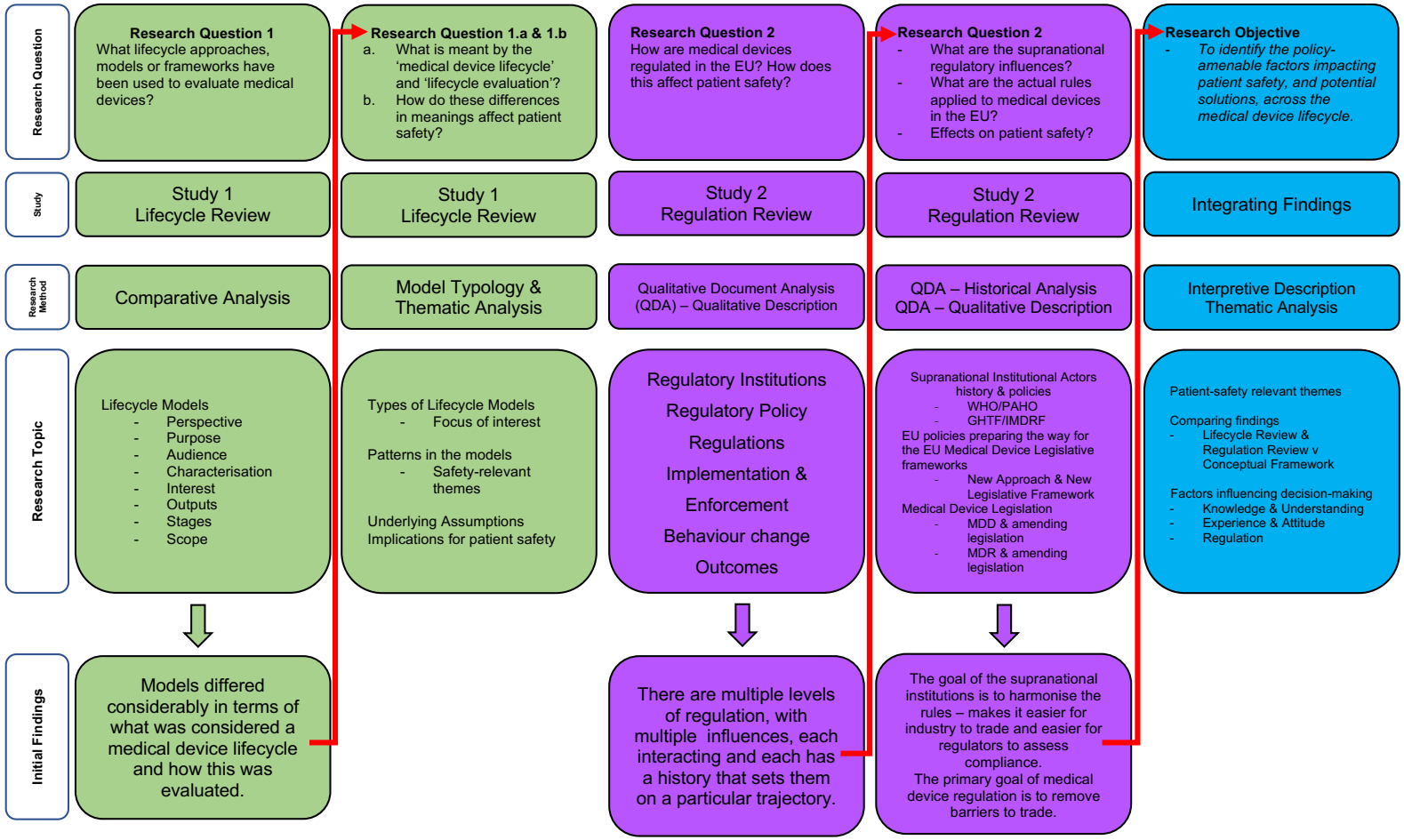
- Best student oral presentation at HTAi 2022 in Utrecht (Lifecycle Review)
- Fundamentals in Medical Device Design and Regulation (FMDDR) 2020 – Badgr. University of Galway.
- Post-grad Certificate in Statistics (Distinction). 2019. Trinity College Dublin.
- Student travel bursary to attend HTAi 2018 in Vancouver.

Memberships

- Member of the International Scientific Program Committee (ISPC), involved in organising the Scientific programme for HTAi 2024 in Seville.
- Application reviewer (2022) for applications for the travel bursaries awarded to attend HTAi 2023.
- Member of the ISCPHM Council, involved in organising the Annual Scientific Meetings in 2022 and 2023. I also proposed and set up the Abstract Review Subgroup in 2023.
- Abstract reviewer for the ISCPHM 2024 conference poster/oral presentations.
- Collaborated with a group at the KCE to review the clinical evidence available for medical devices and medicines when they are first placed on the market or seek public reimbursement. Report available at: https://kce.fgov.be/en/about-us/press-release/evidence-gaps-for-drugs-and-medical-devices-at-market-entry-in-europe-and-potential-solutions; and worked with them to write an invited article on the same topic related to orphan devices or rare diseases, currently in press.
- Was a member of the International Initiatives on the Assessment of the Value of Medical Technologies (IIAVMT), a project group working under the auspices of the International Society of Pharmacoeconomic and Outcomes Research (ISPOR), the work was discontinued when the project leader left ISPOR at the end of 2020.
- Worked with a research group at Bocconi University, participated in conducting interviews with key informants, audio recorded, transcribed, and summarised these for the research team, forming a significant part of the data for a published article.[509]
- Prepared a literature review study protocol, gathered data, and prepared a data collection/abstraction tool for a group involved with the Irish National Orthopaedic Registry (INOR)
- Member of the information retrieval, medical devices, public health, and hospital-based HTA special interest groups in HTA.

14.2. Summary of research linking the research questions to the methods

Aim: To identify policy-amenable factors to address gaps in medical device safety at different stages in the lifecycle.



14.3. Lifecycle Model Characteristics

Model	Device Type	Process Type	Evaluation Type	Model Type	Data Type	QA Score	Year 1st reference of model
Baldock-NPD	Innovation – Product	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Model	Qualitative	0	1960
DOI	Innovation	A logic used to explain a causal relationship in a variance theory	Exploratory and/or Explanatory	Theory	Quantitative	2	1962
PLC	Product	A sequence of events that describe how things change over time	Prescriptive	Model	Quantitative	1	1930
Bass	Product	A logic used to explain a causal relationship in a variance theory	Predictive	Model	Quantitative	2	1963
IRP	Innovation – Policy	A sequence of events that describe how things change over time	Exploratory and/or Explanatory	Model	Qualitative	1	1979
7Sm-IC	Innovation – Health Technology	A sequence of events that describe how things change over time	Descriptive	Model	Mixed	1	1981
BAH-NPD	Product	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Model	Qualitative	0	1982
BLC	Business	Combines both a sequence of events that describe how things change over time and a category of concepts that refer to actions of individuals or organisations	Prescriptive	Framework	Qualitative	1	1982
ILC	Industry	A sequence of events that describe how things change over time	Exploratory and/or Explanatory	Model	Quantitative	2	1982
CK-NPD	Innovation – Product	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Model	Qualitative	2	1980
Norton-Bass	Product	A logic used to explain a causal relationship in a variance theory	Predictive	Model	Quantitative	2	1987
SG-CK-NPD	Product	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Model	Qualitative	2	1990
G-Bass-M	Product	A logic used to explain a causal relationship in a variance theory	Predictive	Model	Quantitative	2	1994
TRL	Technology	A sequence of events that describe how things change over time	Descriptive	Model	Qualitative	0	1995
MDDP	Medical Devices	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Model	Qualitative	0	1997
4S-IEE	Health Technology	Combines both a sequence of events that describe how things change over time and a category of concepts that refer to actions of individuals or organisations	Prescriptive	Framework	Qualitative	0	1997
VA-NPD	Medical Devices – assistive	A category of concepts that refer to actions of individuals or organisations	Descriptive	Model	Qualitative	1	1997
TPLC	Medical Devices	A category of concepts that refer to actions of individuals or organisations	Descriptive	Framework	Qualitative	0	1999

RE-AIM	Health Technology – Public Health intervention	A category of concepts that refer to actions of individuals or organisations	Descriptive	Framework	Mixed	1	1999
TALC	Technology	A sequence of events that describe how things change over time	Prescriptive	Model	Quantitative	1	1991
MDLS	Medical Devices	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Framework	Qualitative	1	1999
HCTLC	Medical Devices	A category of concepts that refer to actions of individuals or organisations	Descriptive	Framework	Qualitative	0	2003
SUHCD	Health Technology	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Model	Qualitative	2	2004
DDDII	Innovation – Health Technology	A logic used to explain a causal relationship in a variance theory	Exploratory and/or Explanatory	Theory	Quantitative	3	2004
TALC-CAHF	Technology	A sequence of events that describe how things change over time	Predictive	Framework	Quantitative	2	2004
SG-MDDP	Medical Devices	A category of concepts that refer to actions of individuals or organisations	Descriptive	Model	Qualitative	1	2009
IEF	Industry	A sequence of events that describe how things change over time	Exploratory and/or Explanatory	Framework	Mixed	2	2009
IRM-TRL	Technology	A sequence of events that describe how things change over time	Descriptive	Model	Qualitative	0	2009
IDEAL	Innovation – Surgery	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Framework	Qualitative	0	2009
EIM-2DA	Innovation – Surgery	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Model	Qualitative	2	2010
TLC	Health Technology	A sequence of events that describe how things change over time	Descriptive	Model	Mixed	0	2010
IC+	Product	A logic used to explain a causal relationship in a variance theory	Descriptive	Model	Mixed	0	2010
MDLC	Medical Devices	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Framework	Qualitative	0	2011
Bhuiyan-NPD	Innovation – Product	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Framework	Qualitative	1	2011
USVP	Business	A sequence of events that describe how things change over time	Exploratory and/or Explanatory	Framework	Qualitative	2	2007
WW-IC	Innovation – Surgery	Combines both a sequence of events that describe how things change over time and a category of concepts that refer to actions of individuals or organisations	Prescriptive	Framework	Qualitative	0	2013
IC	Innovation – Product	Combines both a sequence of events that describe how things change over time and a category of concepts that refer to actions of individuals or organisations	Prescriptive	Model	Qualitative	0	2013
HCanada-MDRegLC	Health Technology	A category of concepts that refer to actions of individuals or organisations	Descriptive	Framework	Qualitative	0	2012

TGA-MDRegLC	Medical Devices	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Framework	Qualitative	0	2014
RxLCF	Innovation – Surgery	A sequence of events that describe how things change over time	Prescriptive	Framework	Mixed	0	2014
PrLC	Technology	A sequence of events that describe how things change over time	Descriptive	Model	Qualitative	0	2014
ELC	Medical Devices – Equipment	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Model	Qualitative	0	2005
IDEAL-D	Medical Devices	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Framework	Qualitative	1	2016
PILC	Innovation – Product	A category of concepts that refer to actions of individuals or organisations	Descriptive	Framework	Qualitative	0	2016
nHTLC4I	Innovation – Health Technology	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Model	Qualitative	1	2017
OIM-DA	Medical Devices – Orthopaedic implantables	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Model	Qualitative	1	2017
HTLC	Health Technology	Combines both a sequence of events that describe how things change over time and a category of concepts that refer to actions of individuals or organisations	Prescriptive	Model	Qualitative	0	2017
NASSS	Innovation – Health Technology	A logic used to explain a causal relationship in a variance theory	Predictive	Theory	Quantitative	3	2017
IRM-SaMDDP	Medical Devices – Software	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Framework	Qualitative	1	2014
EUnetHTA-MDLC	Health Technology	A category of concepts that refer to actions of individuals or organisations	Descriptive	Framework	Qualitative	0	2018
FDA-MDRegLC	Medical Devices	A category of concepts that refer to actions of individuals or organisations	Descriptive	Framework	Qualitative	0	2018
Swissmedic-MDRegLC	Medical Devices	A category of concepts that refer to actions of individuals or organisations	Prescriptive	Framework	Qualitative	0	2017

14.4. Study characteristics of text chosen as the representative text for the lifecycle models

Model	Paper	Author/Proposer	Publication period	Geographical region	Publication Category	Funding/support or COI declared
Baldock-NPD	How to introduce a new product	Baldock	1960-1969	Americas	Conference/ Presentation	None declared
DOI	Diffusion of Innovations	Rogers	1960-1969	Americas	Book	None declared
PLC	Exploiting the Product Life Cycle	Levitt	1960-1969	Americas	Magazine	None declared
Bass	A new product growth for model consumer durables	Bass	1960-1969	Americas	Journal article	None declared
IRP	Life Histories of Innovations: How New Practices Become Routinized	Yin	1980-1989	Americas	Journal article	Funding/ support declared
7Sm-IC	From "Promising Report" to "Standard Procedure": Seven Stages in the Career of a Medical Innovation	McKinlay	1980-1989	Americas	Journal article	Funding/ support declared
BAH-NPD	New product management for the 1980's	Booz, Allen & Hamilton	1980-1989	Americas	Book	Uncertain
BLC	Stages of Growth	Galbraith	1980-1989	Americas	Journal article	Personal interests stated
ILC	Time Paths in the Diffusion of Product Innovations	Gort & Klepper	1980-1989	Americas	Journal article	Funding/ support declared
CK-NPD	An Investigation into the New Product Process: Steps, Deficiencies, and Impact	Cooper & Kleinschmidt	1980-1989	Americas	Journal article	Funding/ support declared
Norton-Bass	A diffusion theory model of adoption and substitution for successive generations of high-technology products	Norton & Bass	1980-1989	Americas	Journal article	None declared
SG-CK-NPD	Stage-gate systems: A new tool for managing new products	Cooper	1990-1999	Americas	Journal article	None declared
G-Bass-M	Why the Bass Model Fits without Decision Variables	Bass, Krishnan, & Jain	1990-1999	Americas	Journal article	None declared
TRL	Technology Readiness Levels. A White Paper	Mankins	1990-1999	Americas	Academic publication	None declared
MDDP	Design Control Guidance for Medical Device Manufacturers	FDA	1990-1999	Americas	Regulatory guidance	Funding/ support declared
4S-IEE	The iterative use of economic evaluation as part of the process of health technology assessment	Sculpher, Buxton, & Drummond	1990-1999	Europe	Journal article	Funding/ support declared
VA-NPD	The Department of Veterans Affairs Rehabilitation Research and Development Service's Technology Transfer Process	Sheredos & Cupo	1990-1999	Americas	Journal article	None declared
TPLC	Appendix D. Impact of the Regulatory Framework on Medical Device Development and Innovation. IN: Public Health Effectiveness of the FDA 510(k) Clearance Process	Feigal Jr. for the Institute of Medicine	2010-2019	Americas	Book	Funding/ support declared
RE-AIM	Evaluating the Public Health Impact of Health Promotion Interventions: The RE-AIM Framework	Glasgow, Vogt, & Boles	1990-1999	Americas	Journal article	Funding/ support declared

TALC	Crossing the Chasm	Moore	2000-2009	Americas	Book	Personal interests stated
MDLS	Medical Device Regulations. Global overview and guiding principles	Cheng	2000-2009	International	WHO Guidance	Funding/ support declared
HCTLC	Medical Device Regulations. Global overview and guiding principles.	Cheng	2000-2009	International	WHO Guidance	Funding/ support declared
SUHCD	Designing for Patient Safety: A Review of the Effectiveness of Design in the UK Health Service	Clarkson	2000-2009	Europe	Journal article	Funding/ support declared
DDDII	Diffusion of Innovations in Service Organizations: Systematic Review and Recommendations	Greenhalgh et al	2000-2009	Americas	Journal article	Funding/ support declared
TALC-CAHF	The technology adoption life cycle attractor: Understanding the dynamics of high-tech markets	Meade & Rabelo	2000-2009	Europe	Journal article	Funding/ support declared
SG-MDDP	Stage-gate process for the development of medical devices	Pietzsch et al	2000-2009	International	Journal article	Funding/ support declared
IEF	Developing a Framework for Mapping Industrial Emergence	Phaal et al	2000-2009	Americas	Conference/ Presentation	Funding/ support declared
IRM-TRL	Technology readiness and risk assessments: A new approach	Mankins	2000-2009	Americas	Journal article	None declared
IDEAL	No surgical innovation without evaluation: the IDEAL recommendations	McCulloch et al	2000-2009	Europe	Journal article	Funding/ support declared
EIM-2DA	EAES recommendations on methodology of innovation management in endoscopic surgery	Neugebauer & Becker et al	2010-2019	International	Journal article	Declared no COI
TLC	Introducing new technology safely	Mytton et al	2010-2019	Europe	Journal article	Funding/ support declared
IC+	Innovate the Future: A Radical New Approach to IT Innovation	Croslin	2010-2019	Americas	Book	None declared
MDLC	Development of medical device policies	Velazquez-Berumen	2010-2019	International	WHO Guidance	Funding/ support declared
Bhuiyan-NPD	A framework for successful new product development	Bhuiyan	2010-2019	Americas	Journal article	None declared
USVP	Understanding academic entrepreneurship: Exploring the emergence of university spin-off ventures using process theories	Rasmussen	2010-2019	Europe	Journal article	Funding/ support declared
WW-IC	The Innovation Cycle: A Framework for Taking Surgical Innovation into Clinical Practice	Wright & Weinstein	2010-2019	Americas	Journal article	Declared no COI
IC	The Innovation Cycle	CIRAS	2010-2019	Americas	Website	None declared
HCanada-MDRegLC	Health Product Vigilance Framework. Release Date: 2012-09-12	Health Canada	2010-2019	Americas	Regulatory guidance	None declared
TGA-MDRegLC	Presentation: Life cycle of medical devices	Reeves & Garcia	2010-2019	Australia	Conference/ Presentation	Disclaimer

RxLCF	Beyond the dichotomy: a tool for distinguishing between experimental, innovative and established treatment	Provoost et al	2010-2019	Europe	Journal article	Funding/ support declared
PrLC	NASA Systems Engineering Handbook Rev 2	NASA	2010-2019	Americas	Book	None declared
ELC	Managing the life cycle of medical equipment	Worm (THET)	2010-2019	International	Online resource	Funding/ support declared
IDEAL-D	Adapting the IDEAL Framework and Recommendations for medical device evaluation: A modified Delphi survey	Pennell et al	2010-2019	International	Journal article	Funding/ support declared
PILC	How the new Procurement Directive may contribute to spur innovative purchases in the health sector	Baeyens	2010-2019	Europe	Conference/ Presentation	None declared
nHTLC4I	New Health Technologies: Managing Access, Value and Sustainability	Paris et al	2010-2019	International	Book	Writing support acknowledged
OIM-DA	How should new orthopaedic implants be introduced: an example and recommendations for best practice	Hannan et al	2010-2019	Australia	Journal article	None declared
HTLC	The Life Cycle of Health Technologies. Challenges and Ways Forward	Gutiérrez-Ibarluzea, Chiumente & Dauben	2010-2019	International	Journal article	Declared no COI
NASSS	Beyond Adoption: A New Framework for Theorizing and Evaluating Nonadoption, Abandonment, and Challenges to the Scale-Up, Spread, and Sustainability of Health and Care Technologies	Greenhalgh et al	2010-2019	Europe	Journal article	Funding/ support declared
IRM-SaMDDP	The integration of the risk management process with the lifecycle of medical device software	Pecoraro & Luzi	2010-2019	Europe	Journal article	None declared
EUnetHTA-MDLC	Session 3: Taking a lifecycle approach to EUnetHTA´s work: Current and future collaborations between early dialogue and Relative Effectiveness Assessments	Meyer, Brühl & Omstad	2010-2019	Europe	Conference/ Presentation	Funding/ support declared
FDA-MDRegLC	TPLC - Total Product Life Cycle	FDA	2010-2019	Americas	Online resource	None declared
Swissmedic-MDRegLC	The tasks of Swissmedic - Lifecycle of a medical device	Swissmedic	2010-2019	Europe	Website	None declared

14.5. Table summarising the lifecycle model characteristics

Model	Pub. Year *	Purpose	Audience	Characterisation	Main interest	Outputs (Detailing ...)	Evaluation Timing	Scope - Lifecycle	Scope - Device	Model Archetype
Baldock-NPD	1960	Define actions or activities	Trade & Industry	Development (stages)	What to do to develop a new product	'How to'	Repeated evaluation at each lifecycle stage	Provision	New	NPD
DOI	1962	Explore Influencing or impacted factors	Policymakers	Adoption (pattern)	Influencing factors	Influencing factors	Lifecycle evaluation at a single point in time	Acquisition & Utilisation	New	Diffusion
PLC	1965	Define actions or activities	Trade & Industry	Sales (pattern)	How to influence lifecycle	Influencing factors	Lifecycle evaluation at a single point in time	Provision	Established	Diffusion
Bass	1969	Describe the lifecycle	Trade & Industry	Sales (pattern)	Predicting sales/adoption	Influencing factors	Lifecycle evaluation at a single point in time	Provision	New	Diffusion
IRP	1981	Describe the lifecycle	Policymakers	Adoption (pattern)	Influencing factors	Influencing factors	Separate evaluation of different phases at a single timepoint	Utilisation	New	Diffusion
7Sm-IC	1981	Describe the lifecycle	Policymakers	Adoption (pattern)	Evidence levels	What happens	Separate evaluation of different phases at a single timepoint	Provision & Acquisition & Utilisation	New	Diffusion
BAH-NPD	1982	Define actions or activities	Trade & Industry	Development (stages)	What to do to develop a new product	'How to'	Repeated evaluation at each lifecycle stage	Provision	New	NPD
BLC	1982	Define actions or activities	Trade & Industry	Development (stages)	What to do to develop a new product	'How to'	Separate evaluation of different phases at a single timepoint	Provision	New	NPD
ILC	1982	Describe the lifecycle	Trade & Industry	Development (pattern)	Influencing factors	Influencing factors	Lifecycle evaluation at a single point in time	Provision	New	Diffusion
CK-NPD	1986	Define actions or activities	Trade & Industry	Development (stages)	Performance evaluation	'How to'	Separate evaluation of different phases at a single timepoint	Provision	New	NPD

Norton-Bass	1987	Explore Influencing or impacted factors	Trade & Industry	Sales (pattern)	Influencing factors	Influencing factors	Lifecycle evaluation at a single point in time	Provision	New	Diffusion
SG-CK-NPD	1990	Determine readiness to progress	Trade & Industry	Development (stages)	Performance evaluation	'How to'	Repeated evaluation at each lifecycle stage	Provision	New	NPD
G-Bass-M	1994	Explore Influencing or impacted factors	Trade & Industry	Sales (pattern)	Influencing factors	Influencing factors	Lifecycle evaluation at a single point in time	Provision	All	Diffusion
TRL	1995	Determine readiness to progress	Trade & Industry	Development (stages)	Performance evaluation	Evaluation methods or activities	Repeated evaluation at each lifecycle stage	Provision & Acquisition	New	Hybrid
MDDP	1997	Define actions or activities	Trade & Industry	Development (stages)	Process controls	Regulation	Repeated evaluation at each lifecycle stage	Provision	All	NPD
4S-IEE	1997	Define actions or activities	Policymakers	Adoption (pattern)	Methods for outcomes evaluation	Evaluation methods or activities	Repeated evaluation at each lifecycle stage	Acquisition	New	Outcomes Evaluation
VA-NPD	1997	Determine readiness to progress	Policymakers	Development (stages)	What to do to develop a new product & Methods for outcomes evaluation	What happens	Repeated evaluation at each lifecycle stage	Provision & Acquisition & Utilisation	New	Hybrid*
TPLC	2010	Define actions or activities	HC & General public	Development (stages)	Regulatory requirements & activities	Regulation	Repeated evaluation at each lifecycle stage	Provision & Utilisation	All	Hybrid
RE-AIM	1999	Define actions or activities	Policymakers	Adoption (pattern)	Methods for outcomes evaluation	Evaluation methods or activities	Repeated evaluation at each lifecycle stage	Provision & Acquisition & Utilisation	New	Outcomes Evaluation
TALC	2001	Define actions or activities	Trade & Industry	Sales (pattern)	How to influence lifecycle	Influencing factors	Lifecycle evaluation at a single point in time	Provision	New	Diffusion
MDLS	2003	Define actions or activities	Policymakers	Development (stages)	Regulatory requirements & activities	Regulation	Repeated evaluation at each lifecycle stage	Provision & Utilisation	All	Hybrid
HCTLC	2003	Define actions or activities	Policymakers	Development (stages)	What happens across the lifecycle	What happens	Lifecycle evaluation at a single point in time	Provision & Acquisition & Utilisation	All	Hybrid

SUHCD	2004	Define actions or activities	Healthcare	Development (stages)	What to do to develop a new product & Methods for outcomes evaluation	'How to'	Repeated evaluation at each lifecycle stage	Provision & Acquisition & Utilisation	New	Hybrid*
DDDII	2004	Explore Influencing or impacted factors	Policymakers	Adoption (pattern)	Influencing factors	Influencing factors	Lifecycle evaluation at a single point in time	Acquisition	New	Diffusion
TALC-CAHF	2004	Identify lifecycle stage	Trade & Industry	Sales (pattern)	Identifying where in the lifecycle a technology is	Evaluation methods or activities	Separate evaluation of different phases at a single timepoint	Provision	New	Diffusion
SG-MDDP	2009	Determine readiness to progress	Trade & Industry	Development (stages)	What to do to develop a new product	'How to'	Repeated evaluation at each lifecycle stage	Provision	New	NPD
IEF	2009	Describe the lifecycle	Trade & Industry	Development (pattern)	What happens across the lifecycle	Influencing factors	Separate evaluation of different phases at a single timepoint	Provision	New	Diffusion
IRM-TRL	2009	Determine readiness to progress	Trade & Industry	Development (stages)	Performance evaluation	Evaluation methods or activities	Repeated evaluation at each lifecycle stage	Provision & Acquisition	New	Hybrid
IDEAL	2009	Define actions or activities	Healthcare	Development (stages)	Methods for outcomes evaluation	Evaluation methods or activities	Repeated evaluation at each lifecycle stage	Provision & Acquisition & Utilisation	New	Outcomes Evaluation
EIM-2DA	2010	Identify lifecycle stage	Healthcare	Development (stages)	Methods for outcomes evaluation	Evaluation methods or activities	Repeated evaluation at each lifecycle stage	Provision & Acquisition & Utilisation	New	Outcomes Evaluation
TLC	2010	Describe the lifecycle	Healthcare	Adoption (pattern)	What happens across the lifecycle	What happens	Separate evaluation of different phases at a single timepoint	Provision & Acquisition & Utilisation	All	Outcomes Evaluation
IC+	2010	Explore Influencing or impacted factors	Trade & Industry	Sales (pattern)	What happens across the lifecycle	Evaluation methods or activities	Separate evaluation of different phases at a single timepoint	Provision	New	Diffusion
MDLC	2011	Define actions or activities	Policymakers	Development (stages)	Process controls	'How to'	Separate evaluation of	Provision & Acquisition	All	Hybrid*

							different phases at a single timepoint	& Utilisation & Regulation		
Bhuiyan-NPD	2011	Define actions or activities	Trade & Industry	Development (stages)	Performance evaluation	'How to'	Repeated evaluation at each lifecycle stage	Provision	New	NPD
USVP	2011	Describe the lifecycle	Trade & Industry	Development (stages)	Influencing factors	Influencing factors	Lifecycle evaluation at a single point in time	Provision	New	NPD
WW-IC	2013	Define actions or activities	Healthcare	Development (stages)	Methods for outcomes evaluation	Evaluation methods or activities	Repeated evaluation at each lifecycle stage	Provision & Acquisition & Utilisation	New	Outcomes Evaluation
IC	2013	Define actions or activities	Trade & Industry	Development (stages)	Performance evaluation	'How to'	Repeated evaluation at each lifecycle stage	Provision	New	NPD
HCanada-MDRegLC	2013	Define actions or activities	General public	Development (stages)	Regulatory requirements & activities	Regulation	Repeated evaluation at each lifecycle stage	Provision & Utilisation	All	Hybrid
TGA-MDRegLC	2014	Define actions or activities	Trade & Industry	Development (stages)	Regulatory requirements & activities	Regulation	Repeated evaluation at each lifecycle stage	Provision & Utilisation	All	Hybrid
RxLCF	2014	Identify lifecycle stage	Healthcare	Development (stages)	Identifying where in the lifecycle a technology is	Evaluation methods or activities	Repeated evaluation at each lifecycle stage	Acquisition	New	Outcomes Evaluation
PrLC	2017	Define actions or activities	Policymakers	Development (stages)	What to do to develop a new product & Methods for outcomes evaluation	'How to'	Repeated evaluation at each lifecycle stage	Provision & Acquisition & Utilisation	New	Hybrid*
ELC	2015	Define actions or activities	Healthcare	Health technology management activities	How to perform HTM (highlighting potentially false assumptions & mitigating actions)	Evaluation methods or activities	Repeated evaluation at each lifecycle stage	Acquisition & Utilisation	Establishe d	Diffusion

IDEAL-D	2016	Define actions or activities	Regulators	Development (stages)	Methods for outcomes evaluation	Evaluation methods or activities	Repeated evaluation at each lifecycle stage	Provision & Acquisition & Utilisation	New	Outcomes Evaluation
PILC	2016	Define actions or activities	T&I and HC	Development (stages)	Approaches to integrating innovation into the healthcare system	Regulation	Repeated evaluation at each lifecycle stage	Provision & Acquisition	New	Diffusion
nHTLC4I	2017	Define actions or activities	Policymakers	Development (stages)	Approaches to integrating innovation into the healthcare system	Regulation	Repeated evaluation at each lifecycle stage	Acquisition & Utilisation	New	Diffusion
OIM-DA	2017	Define actions or activities	Healthcare	Development (stages)	Methods for outcomes evaluation	Evaluation methods or activities	Repeated evaluation at each lifecycle stage	Acquisition & Utilisation	New	Outcomes Evaluation
HTLC	2017	Define actions or activities	Policymakers	Development (stages)	Methods for outcomes evaluation	Evaluation methods or activities	Repeated evaluation at each lifecycle stage	Provision & Acquisition & Utilisation	New	Outcomes Evaluation
NASSS	2017	Explore Influencing or impacted factors	Policymakers	Adoption (pattern)	Predicting sales/adoption	Evaluation methods or activities	Separate evaluation of different phases at a single timepoint	Acquisition & Utilisation	New	Diffusion
IRM-SaMDDP	2017	Define actions or activities	Trade & Industry	Development (stages)	What to do to develop a new product	'How to'	Separate evaluation of different phases at a single timepoint	Provision	New	NPD
EUnetHTA-MDLC	2018	Define actions or activities	T&I and HTA	Adoption (pattern)	Methods for outcomes evaluation	Evaluation methods or activities	Repeated evaluation at each lifecycle stage	Provision & Acquisition	New	Outcomes Evaluation
FDA-MDRegLC	2018	Define actions or activities	General public	Development (stages)	Regulatory requirements & activities	Regulation	Repeated evaluation at each lifecycle stage	Provision & Utilisation	All	Hybrid
Swissmedic-MDRegLC	2019	Define actions or activities	T&I and General public	Development (stages)	Regulatory requirements & activities	Regulation	Repeated evaluation at each lifecycle stage	Provision & Utilisation	All	Hybrid

Note: Hybrid* indicates that the model includes a focus on outcomes evaluation as well as either new product development (NPD) and/or diffusion.

14.6. Example of documents in the document archive - Documents saved in the ‘MDD preparatory documents' category in the document archive

Documents in the MDD preparatory documents category	Document Title
CELEX 51991PC0287 EN TXT.pdf	Proposal for a COUNCIL DIRECTIVE concerning medical devices
CELEX 51992AC0086 EN TXT.pdf	Economic and Social Committee Opinion on the proposal for a Council Directive concerning Medical Devices
CELEX 51992PC0356 EN TXT.pdf	Amended proposal for a Council Directive relating to the medical devices
CELEX 51993PC0241 EN TXT.pdf	Re-examined proposal for a COUNCIL DIRECTIVE RELATING TO MEDICAL DEVICES
CELEX_31984L0539_EN_TXT.pdf	COUNCIL DIRECTIVE of 17 September 1984 on the approximation of the laws of the Member States relating to electro-medical equipment used in human or veterinary medicine
CELEX_31989L0686_EN_TXT.pdf	COUNCIL DIRECTIVE of 21 December 1989 on the approximation of the laws of the Member States relating to personal protective equipment
CELEX_31990L0385_EN_TXT.pdf	COUNCIL DIRECTIVE of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices
OJ C 1991 237 FULL EN TXT.pdf	Proposal for a Council Directive concerning medical devices (II Preparatory Acts)
OJ C 1992 150 FULL EN TXT.pdf	Minutes of the sitting of Monday, 11 May 1992: Medical devices (debate) **I, p.18; Medical devices (vote) **I, p.36; Medical devices **I; Proposal for a Council Directive on medical devices (COM(91) 0287 — C3.-0331 /91 — SYN 353), p.103; Legislative resolution (A3-0178/92), p.118.
OJ C 1993 071 FULL EN TXT.pdf	Establishing by the Council of common positions under the cooperation procedure provided for by Article 149 (2) of the Treaty establishing the European Economic Community - The Council has established common positions on the following proposals: 1. Proposal for a Council Directive concerning medical devices 4327/1/93 + ADD 1
OJ C 1993 150 FULL EN TXT.pdf	Minutes of the sitting of Monday, 19 April 1993: Medical devices **II (vote), p.65; Medical devices **II, Decision on the common position established by the Council with a view to the adoption of a Directive concerning medical devices (A3-0088/93), p.116; **II Recommendation of the Committee on Economic and Monetary Affairs and Industrial Policy on the common position established by the Council with a view to the adoption of a Directive concerning medical devices (C3-0105/93 — SYN 353), p.8; Medicinal products **II (debate), p.16 (this was actually on medical devices).
OJ JOC_1992_150_R_0001_01 EN TXT.pdf	Minutes of the sitting of Monday, 11 May 1992: **I REPORT of the Committee on Economic and Monetary Affairs and Industrial Policy on the proposal from the Commission to the Council for a Directive concerning medical devices (COM(9 1)0287 — C3 0331/91 — SYN 353): Medical devices (debate) **I, p.18.
OJ JOC_1992_150_R_0028_01 EN TXT.pdf	Minutes of the sitting of Monday, 13 May 1992: Medical devices (vote) **I, p.36.

14.7. Documents eligible for inclusion in the Regulation Review

Table 14.1. Documents relevant for reviewing Supranational Intervention

Supranational Intervention	
Question	**Documents suited to answering the question(s)**
What international or supranational bodies seek to influence medical device regulation?	Websites of regional, or international organisations or institutions seeking to influence medical device regulation or healthcare or trade related to medical devices (e.g. the World Health Organization (WHO), the Global Harmonization Task Force (GHTF), etc).
What mechanisms do they use to influence medical device regulation?	Consensus Statements; Guidelines; Standards; Trade agreements;
What sort of documents would provide insight into how they work to achieve their goal?	Minutes of meetings; meeting agendas; internal memoranda; press releases; processual/procedural documents; statistical and other reports.

Table 14.2. Documents relevant for reviewing State Intervention

State Intervention			
Step in the regulatory process		**Question**	**Documents suited to answering the question(s)**
A	Regulatory Institution => Rule-making institutions in the EU	1. What bodies or institutions have responsibility for making the rules for regulating medical devices in the EU? 2. What is their organisational structure and make-up?	Legislation establishing who has the authority to legislate (e.g. treaties); policy documents; historical summaries
B	Regulatory Policy => Rule-making process in the EU	1. What type of 'rules' do they make? 2. What is the decision-making process for making rules? 3. Who can influence this decision?	Legislation describing rules of procedure legally required of the legislative bodies; policy documents guiding legislators; institutional summaries of the procedural rules
C	Regulation => Rules, i.e. Legal framework for medical devices	1. What are the key 'rules' regulating medical devices in Ireland and the EU? (i.e. the specific regulatory instruments such as directives, regulations, guidelines, standards, etc.) 2. What are the core elements of the 'rule'? 3. How have these changed over time?	Primary and secondary (i.e. implementing) legislation; standards; guidance documents; forms required for compliance
D	Implementation => Rule-enforcing bodies & their processes	1. How is the MDD implemented? 2. Who are the stakeholders involved in its implementation? 3. What are the steps that each of the stakeholders (regulators) must follow in order to implement and comply with the regulations?	Legislation governing regulatory bodies; websites of the regulatory bodies; requirements and guidance provided by regulatory authorities; websites of supranational associations of regulators and their documentation (e.g. the Notified Bodies Operations Group, NBOG; Competent Authorities for Medical Devices, CAMD; GHTF and IMDRF).
E	Behaviour change => The steps that a manufacturer must take to market their medical device	1. What behaviours are expected to result? 2. What are the steps that each of the stakeholders (targets) must follow in order to comply with the regulations? 3. What are the steps in the CE marking process?	Most of this information is likely to be confidential and inaccessible, so the following may have to suffice as proxies: Designating or competent authority reports or evaluations of compliance; application forms for conformity assessment and other requirements stated on notified body

			(NB) websites such as the National Standards Authority of Ireland (NSAI); industry resources provided to support industry to comply.
F	Intermediate outcomes => CE marking ➔ Market access ➔ Patient access	1. What evidence would indicate that technical barriers to trade had been removed or minimised? 2. What potential indicators might exist to measure market access and patient access? 3. What data is available for these indicators? (Is it accessible?)	Trade reports; international sources of trade and/or healthcare statistics; press releases by industry of new product launches; industry sales reports; notice of contracts awarded on the European or national eTenders websites by public procurers; procurement data or reports; HTAs of novel devices, and official announcements of national funding decisions for novel medical devices; academic literature.
G	Ultimate outcomes => The goals of the regulation	1. What evidence would indicate changes in the level of trade in medical devices? 2. What evidence would indicate changes in the level of safety (including effectiveness) of medical devices?	Industry reports; trade reports. When this research started there was no single cross-European source of data on patient outcomes, including adverse events, and there still isn't. EUDAMED is being developed as a source of this information, but it is still in development and based on what is currently publicly available on it is unlikely to provide much detail in the future. One source of cross-EU data on medical device related adverse events is the annual summary report on the national competent authority reports (NCARs) on serious incidents. Other sources include the individual NCA databases of field safety notices (FSNs) and corrective actions (FSCAs) taken by manufacturers, but these only apply to the NCAs own jurisdiction.

Table 14.3. Rules of precedence - Choosing between documents as appropriate to the regulatory step

Supranational Interventions & Influences		
Element	**Target Source**	**Choose documents**
Who: What supranational or international organisations have influenced the development of the EU regulatory framework?	The WHO and IMDRF were considered to be potentially relevant supranational influences, whilst others considered to have significant influence were identified through reference to them in official EU documents or meeting agendas or minutes from the IMDRF.	Unofficial internal documents not intended for the public > Official documents intended for the public
How: How do actors attempt to influence medical device regulation at a supranational level, what mechanisms do they use? And what sort of documents would provide insight into how they work to achieve their goal?	Influence at an inter/supranational level usually involves the coming together of key people with a common agenda (although their reasons for this may differ), trying to further that through cooperation. For example, standardising the approach to regulating medical devices raises the standards and safety of medical devices in some (previously unregulated) parts of the world, but it also removes barriers to trade by reducing the work required to meet those regulations if they are the same everywhere.	Confidential correspondence within or between members of relevant institutions > Internal memoranda & reports > Agendas & minutes of meetings or technical documents > Publications > Public presentations

What: What are the rules that they use to influence regulation?		These are the documents that more directly impact on medical device regulation.	Supranational legislation > international agreements signed and ratified by the EU > Institutional guidance > Institutional resolutions
State Intervention			
Step in the regulatory process		**Key Question**	**Choose documents**
A	Regulatory Institution	Who are the legislators?	Treaties > EU public information
B	Regulatory Policy	How is legislation enacted?	Legislative procedures used for medical devices > Guidance on the legislative procedures in general
C	Regulation	What are the rules?	EU Legislation > National Law > non-legislative documents
D	Implementation	How are they implemented?	Requirements of regulators (e.g. notified bodies) > Standards > MEDDEVs > Codes of practice
E	Behaviour change	How does industry behave to comply?	Requirements of regulators (e.g. notified bodies) > regulatory guidance or advice to industry > industry reports
F	Intermediate outcomes	What are the intermediate outcomes?	Statistics & primary research > Statistical Reports > Narrative Reports (on market access and user or patient access)
G	Ultimate outcomes	What are the ultimate outcomes?	Statistics & primary research > Statistical Reports > Narrative Reports (on trade, and patient outcomes)

14.8. Key documents explored

Table 14.4. Key documents reviewed and supporting documents

Supranational Interventions & Influences		
Institution	**Key documents**	**Supporting documents**
WHO	• WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices[510]; • Medical device regulations: global overview and guiding principles[97];	Webpages and other documents in the
IMDRF	• Guidance documents: Medical Devices: Post Market Surveillance: National Competent Authority Report (NCAR) Pilot Plan; • Medical Devices: Post Market Surveillance: National Competent Authority Report (NCAR) Pilot Plan (IMDRF/NCAR WG/N30 FINAL 2015); • Implementing Material (IMDRF/NCAR WG/N31 FINAL 2015); • Medical Devices: Post-Market Surveillance: National Competent Authority Report Exchange Criteria and Report Form (IMDRF/NCAR WG/14FINAL: 2017 (Edition 2)	IMDRF Management Committee Meeting outcome statements; Public presentations; Website pages
GHTF	• Guidance documents: The GHTF Regulatory Model (GHTF/AHWG-GRM/N1R13:2011); • Principles of Conformity Assessment for medical devices (GHTF/SG1/N78/2012);	Website pages

		• Medical Devices: Post-Market Surveillance: National Competent Authority Report Exchange Criteria and Report Form (GHTF/SG2/N79R11:2009);	
WTO		Website pages	• The General Agreement on Tariffs and Trade (GATT 1947) {Note – this document is more authentic and credible than the WTO webpages, but time did not allow for this to be explored in detail, hence it is only a supporting document.}
PAHO			• A guide for the development of medical device regulations; • A model regulatory program for medical devices an international guide.
Trade Associations		Website pages	https://www.advamed.org/
State Intervention			
Key Institutions		**Key documents**	**Supporting documents**
A	Institutions of the EU listed below (Step B)	Treaties (listed in Table 8.22) also relevant to Step B	EU public information
B	The Commission, the Council, the European Parliament, and their predecessors	• Council Decision of 13 July 1987 laying down the procedures for the exercise of implementing powers conferred on the Commission (87/373/EEC); • Council Decision of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission (*)(1999/468/EC); • Council **resolution** of 7 May 1985 concerning a new approach to technical harmonization and standardization; • Certain Treaties; • Council Decision of 13 December 1990 concerning the modules for the various phases of the conformity assesment procedures which are intended to be used in the technical harmonization directives (90/683/EEC); • Decision No 768/2008/EC of the European Parliament and of the Council of 9 July 2008 on a common framework for the marketing of products, and repealing Council Decision 93/465/EEC; • Regulation (EC) No 764/2008 of the European Parliament and of the Council of 9 July 2008 laying down procedures relating to the application of certain national technical rules to products lawfully marketed in another Member State and repealing Decision No 3052/95/EC	Guidance on the legislative procedures in general from EU website pages (particularly on the Cooperation procedure and the Ordinary Legislative Procedure); Standard Rules of Procedure for Committees Rules of Procedure for the [Name of the Committee] Committee (2011/C 206/06);
C	Regulation	• COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices (MDD). Amended by: • Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998;	Legislation referred to in the MDD, including those related to the implementing powers of the Commission, modules for conformity assessment,

		• Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000; • Directive 2001/104/EC of the European Parliament and of the Council of 7 December 2001; • Regulation (EC) No 1882/2003 of the European Parliament and of the Council of 29 September 2003; • Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007. • Article 100a of the Treaty of Rome as amended by the Single European Act. • Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC	
D	Designating Authorities, Competent Authorities, Notified Bodies, Accreditation Bodies, and their umbrella organisations (the Notified Bodies Operations Group (NBOG), Competent Authorities for Medical Devices (CAMD), TeamNB, and European Accreditation (EA)).	• The websites of the regulatory authorities involved in implementation. • COUNCIL DECISION of 22 July 1993 concerning the modules for the various phases of the conformity assessment procedures and the rules for the affixing and use of the CE conformity marking, which are intended to be used in the technical harmonization directives; • Notified Bodies Operations Group (NBOG) Best Practice Guides (e.g. Certificates issued by Notified Bodies with reference to Council Directives 93/42/EEC on medical devices (MDD); • 98/79/EC on in vitro diagnostic medical devices (IVDD); • 90/383/EEC on active implantable medical devices (AIMDD).	• COMMISSION NOTICE The 'Blue Guide' on the implementation of EU products rules 2016 (2016/C 272/01)
E	Specific NBs (e.g. NSAI, BSI, Tüv Süd); EUDAMED	• NSAI CE marking assessment application forms; • Conformity assessment certificates issued by NBs; • Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED) (GHTF/SG1/N011/2008)	• Industry peer guidance; • the MEDDEVs; • GHTF & IMDRF guidance documents. • MDCG Guidance
F	Intermediate outcomes		NA
G	Ultimate outcomes	NCAR Summaries	Guidelines for NCARs:
The Rules			
Original legal framework		**Key documents**	**Supporting documents**
		MDD & its amending legislation	All the above

14.9. Legislation amending or implementing the MDR

Corrigenda

1. Corrigendum of 27 December 2019 to Regulation (EU) 2017/745 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Directives 90/385/EEC and 93/42/EEC.
2. Corrigendum of 5 May 2019 to Regulation (EU) 2017/745 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Directives 90/385/EEC and 93/42/EEC.

Amending Acts

1. Regulation (EU) **2024/568** of the European Parliament and of the Council of 7 February 2024 **on fees and charges payable to the European Medicines Agency**, amending Regulations (EU) 2017/745 and (EU) 2022/123 of the European Parliament and of the Council and repealing Regulation (EU) No 658/2014 of the European Parliament and of the Council and Council Regulation (EC) No 297/95
2. Regulation (EU) **2023/607** of the European Parliament and of the Council of 15 March 2023 amending Regulations (EU) 2017/745 and (EU) 2017/746 as regards the **transitional provisions** for **certain medical devices** and in vitro diagnostic medical devices (Text with EEA relevance)
3. Regulation (EU) **2020/561** of the European Parliament and of the Council of 23 April 2020 amending Regulation (EU) 2017/745 on medical devices, as regards the **dates of application** of certain of its provisions (Text with EEA relevance)

Implementing Act

1. Commission Implementing Regulation (EU) **2023/1194** of 20 June 2023 amending Implementing Regulation (EU) 2022/2346 as regards the **transitional provisions** for certain products without an intended medical purpose **listed in Annex XVI** to Regulation (EU) 2017/745 of the European Parliament and of the Council.
2. Commission Implementing Regulation (EU) **2022/2347** of 1 December 2022 laying down rules for the application of Regulation (EU) 2017/745 of the European Parliament and of the Council as regards **reclassification** of groups of certain **active products without an intended medical purpose**.
3. Commission Implementing Regulation (EU) **2022/2346** of 1 December 2022 laying down **common specifications** for the groups of products without an intended medical **purpose listed in Annex XVI** to Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices.
4. Commission Implementing Regulation (EU) **2021/2226** of 14 December 2021 laying down rules for the application of Regulation (EU) 2017/745 of the European Parliament and of the Council as regards **electronic instructions for use** of medical devices.
5. Commission Implementing Regulation (EU) **2021/2078** of 26 November 2021 laying down rules for the application of Regulation (EU) 2017/745 of the European Parliament and of the Council as regards the European Database on Medical Devices (**Eudamed**).
6. Commission Implementing Regulation (EU) **2020/1207** of 19 August 2020 laying down rules for the application of Regulation (EU) 2017/745 of the European Parliament and of the Council as regards **common specifications for the reprocessing of single-use devices**.
7. Commission Implementing Decision (EU) **2019/1396** of 10 September 2019 laying down the rules for the application of Regulation (EU) 2017/745 of the European Parliament and of the Council as regards the **designation of expert panels** in the field of medical devices.
8. Commission Implementing Decision (EU) **2019/939** of 6 June 2019 **designating issuing entities** designated to operate a system for the assignment of Unique Device Identifiers (**UDIs**) in the field of medical devices.
9. Commission Implementing Regulation (EU) **2017/2185** of 23 November 2017 on the **codes for the designation of notified bodies** in medical devices under Regulation (EU) 2017/745 and in vitro diagnostic medical devices under Regulation (EU) 2017/746.

Delegated Acts

1. Commission Delegated Regulation (EU) **2023/2197** of 10 July 2023 amending Regulation (EU) 2017/745 of the European Parliament and of the Council, as regards the **assignment of Unique Device Identifiers** for **contact lenses**
2. Commission Delegated Regulation (EU) **2023/502** of 1 December 2022 amending Regulation (EU) 2017/745 of the European Parliament and of the Council as regards **the frequency of complete re-assessments of notified bodies.**