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Comparative Analysis of Artificial Intelligence on Medical Device Regulations and Legislation in US and EU

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Abstract

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The following manuscript is a scoping literature review which provides a comparative narrative analysis of the impacts of artificial intelligence (AI) applications on medical device (MD) technology and its subsequent legislation and regulations, in the United States of America and the European Union (EU) member countries. The objective of this research study is to compare and outline the current regulatory policies in the US and EU concerning the implementation of artificial intelligence in medical technology and health technology. The methodology principles used to conduct this literature review are based upon the Levac six-stage methodology framework; a more comprehensive version of the Arksey & O'Malley scoping literature review guidelines.

The scope of the study is contained to two of the world's largest and well-known regulatory agencies; the United States government agency, Food and Drugs Administration (FDA) and the European Union's Medical Devices Regulation (MDR) concerning Regulation (EU) 2017/745. The filtered and final results of three electronic databases (ScienceDirect, ProQuest Central and PubMed) yielded a total of 30 hits, from which 15 articles (journal article, review article and research article) were chosen to synthesis the answer to the main research question; "How does artificial intelligence impact the United States Food and Drugs Administrations medical device legislation and the EU Medical Device Regulation?".

The findings showcase that industry specialists endorse a complete system overhaul to better regulate AI algorithms in the case of both regulatory authorities, the United States government agency, FDA, and the EU MDR.
In conclusion, more scientific studies need to be conducted on the field of AI/ML-based medical devices in regard to its regulatory approval process and framework.

Keywords: artificial intelligence, medical device regulation, medical device legislation, Regulation (EU) 2017/745, FDA, MDR, scoping review

Tiivistelmä

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Tämä kyseinen opinnäytetyö on scoping-kirjallisuuskatsaus, joka antaa vertailevan analyyttisen kertomuksen tekoälyn sovellusten vaikutuksista lääketieteellisiin laitteisiin ja niiden lainsäädäntöihin Yhdysvalloissa ja Euroopan unionin (EU:n) jäsenmaissa. Tutkimuksen tavoitteena on verrata ja hahmotella Yhdysvaltojen ja EU:n nykyisiä lainsäädäntöjä, jotka koskevat tekoälyalgoritmin sovellusta lääketieteellisissä laitteissa ja terveysteknologiassa. Tämän kirjallisuuskatsauksen menetelmä perustuu Levacin kuusivaiheiseen viitekehykseen ja on kattavampi versio Arksey & O'Malleyn kirjallisuuden ohjesäännöistä.

Tutkimus kattaa kaksi maailman suurinta ja tunnetuinta virastoa: Yhdysvaltain elintarvike- ja lääkevirasto, Food and Drugs Administration (FDA) ja Euroopan unionin lääketieteellisten laitteiden asetus (MDR), mikä koskee asetusta (EU) 2017/745. Tutkimuksen kolme valittua sähköisen tietokannan (ScienceDirect, ProQuest Central ja PubMed) suodatettua ja lopullista tulosta tuotti yhteensä 30 osumaa, joista valittiin 15 artikkelia (aikakauslehtiartikkeli, arvosteluartikkeli ja tutkimusartikkeli) vastaamaan opinnäytetyön tutkimuskysymykseen "Miten tekoäly vaikuttaa Yhdysvaltain elintarvike- ja lääkevirastojen lääketieteellisten laitteiden lainsäädäntöön (FDA) ja EU:n lääkinnällisten laitteiden asetukseen (MDR)?".

Tulokset osoittavat, että alan asiantuntijat tukevat täydellistä järjestelmän uudistusta tekoälyalgoritmien regulaation parantamiseksi molempien sääntelyviranomaisten, Yhdysvaltain valtion viraston, FDA:n että EU:n MDR:n tapauksessa. Johtopäätöksenä voidaan todeta, että tekoälypohjaisten lääkinnällisten laitteiden regulaatiossa on tehtävä enemmän tieteellisiä tutkimuksia, jotta voidaan saada konkreettinen kuva tekoälyn vaikutuksista lääkinnällisten laitteiden säätelyyn.

Avainsanat: tekoäly, lääketieteellisten laitteiden lainsäädännöt, EU-regulaatio 2017/745, FDA, MDR, scoping katsaus

Contents

List of Abbreviations

AI	Artificial intelligence
AGI	Artificial general intelligence
ANSI	American National Standards Institute
CAGR	Compound Annual Growth Rate
CE	Conformité Européenne
CEN	European Committee for Standardization
EHR	Electronic Health Record
EU	European Union
EUDAMED	European Database on Medical devices
FDA	Food and Drugs Administration (USA)
GDPR	General Data Protection Regulation
GHTF	Global Health Task Force
GMP	Good Manufacturing Practice
IEC	International Electrotechnical Commission
IMDRF	International Medical Device Regulator Forum
IoT	Internet of Things
ISO	International Organization for Standardization

IVD	In vitro device; in vitro diagnostics
MD	Medical Devices
MDCG	Medical Device Coordination Group
MDR	Medical Device Regulations
MDSW	Medical Device Software
ML	Machine Learning
NLP	Natural Language Processing
PICO (T)	Question format (population, intervention, control, and outcomes)
PM	Precision Medicine
QMS	Quality Management System
RMP	Risk Management Policy
SaMD	Software as a Medical Device
UDI	Unique Device Identification
WHA	World Health Assembly
WHO	World Health Organization

1 Introduction

Artificial intelligence (AI) applications in healthcare have garnered a large amount of attention. With interest in artificial intelligence in healthcare soaring, investors in 2019 have poured 4 billion USD into the sector. (CB Insights, 2021) The current information based on last year's data estimates the global medical device market size to be around 432 billion USD. Regardless of the unpresented global impact of Covid-19 the market size is projected to reach 455 billion USD in 2021. (Fortune Business Insights, 2021)

There are several research studies being carried out to measure the benefits of artificial intelligence in the field such as precision medicine (PM), population health, and natural language processing (NLP), as these areas have the potential to transform patient care. For example, AI technology of visual tasks, known as computer vision, has created a large amount of interest in visually oriented medical specialties such as radiology, pathology, ophthalmology, and dermatology. (Kulkarni et al., 2020) The reason behind modern AI development is because of the large quantity of data that has been gathered in widely available digital datasets. These datasets are used in deep learning to train algorithms to perform specific tasks. (Davenport & Kalakota, 2019)

The application of AI in the fields of medicine and health technology is a solution that can potentially offer early diagnoses and targeted treatments to improve patient out-comes. It has the definitive potential to enormously benefit healthcare services by driving efficiency and effectiveness. (Bohr & Memarzadeh, 2020) This manner of personalized medicine approach is mainly acquired through primary specialties of clinical genetics and clinical molecular genetics. (Mason-Suarez et al., 2016) According to Goldenberg et al., AI is already transforming the practice of medicine by way of providing medical professionals the tools to accurately diagnose patients, make better predictions on patient's future health and optimize specialized treatments. (Ahmad et al., 2021) (Goldenberg et al., 2019).

The healthcare industry is ripe for AI development due to its rich datasets. (Golden, 2017) Personalized medicine is a major objective on multiple medical fields including ophthalmology. By designing an end-to-end medical AI system, it will lead to further accomplishments on PM, which could objectively improve both basic and transitional cancer research. This may be far in the future but even now, the brittleness of building and defining correct frameworks for these systems causes vital concerns. The importance of acknowledging and ensuring vigorous quality control including recognizing the possibility of mathematical errors in machine learning algorithm data inputs will need to be ensured by regulations. (Ash et al., 2004) On of the ways to build consumer trust and revoke safety concerns is to take the responsibility of regulatory enforcement to the product developers. Such is the case for the US governmental agency of Food and Drugs Administration (FDA), where a preliminary workshop discussion held in 2017 lead to the announcement of a pilot certification approach to inspect AI developers and products called the Digital Health Software Precertification (Pre-Cert) Program, in 2019. The updated 2020 manual published highlights of the findings that have been tested under the Pre-Cert Pilot Program and how it will be utilized in the future to regulate SaMD (Software as a Medical Device) products including AI software. (FDA, 2020) This is done to establish transparency of organizations and build trust in the SaMD products. It is imperative that trust must be ensured in medical devices and quality, for efficiency and effectiveness must be held to high standards otherwise it will decrease the anticipated utility of AI in the public.

At the present moment, the approval, and regulations of AI in medical devices is conducted differently in the US and the EU. Both use healthcare policies that categorize medical devices according to risk factors (I, II, III). The centralized FDA uses a three-way approval path to device clearances: the premarket approval pathway (highly rigorous review for high-risk devices), the de-novo premarket review (for low and moderate-risk devices), and the 510(k) pathway. (Hwang et al., 2019) On the other hand, the de-centralized EU lets private accredited organizations i.e., Notified Bodies assess the conformity of MD products and assign them a Conformité Européenne (CE) mark before being

placed in the market. The CE mark is given to regulated medical devices that verify the requirements of specific legislation are upheld to standards. For now, the regulation of AI software in MD technology is up in the air.

In the past years, there have been discussion forums and white papers related to this subject, for example the European Commission's white paper on AI. (European Commission, 2020) In this thesis, the focus is on the recent information available including grey literature (or grey literature) which are produced by organizations outside of academic or commercial publishing and distributing channels. (Schöpfel & Farace, 2010) The main point of this study is the charting of scientific data which focus or consider the impact of AI-based medical devices have on European Union regulations and USA legislatives as they reach the consumer market. The best way to become informed on the subject matter is by searching the literature available on multidisciplinary databases and conducting a literature review. And so, the objective of this thesis is to perform a scoping review which answers the following research question, "How does artificial intelligence impact the United States Food and Drugs Administrations medical device legislation and the EU Medical Device Regulation?".

2 Methodology

The first part of this thesis is a narrative literature which explores the background of the scoping study, the United States and EU member states medical device regulations/legislation framework and gives an insight into the future of artificial intelligence applications in the field of medical technology and medical science. The second part of this thesis is a scoping literature review, is conducted by utilizing elements taken from the well-known literature research study method of systematic literature reviews. The methodological framework of systematic literature review is consulted when answering a focused research question and employing a comprehensible, reproducible search strategy.

However, in this case the literature review study cannot be employed by simply using the conservative systematic literature review, where both published and unpublished studies are identified, but only the relevant studies are selected and are critically appraised. The subject matter, due to its rapid development at the present moment, needs more content than what can be accessed from peer-reviewed scientific research articles/reviews and so the selected study method in this case is the scoping literature review research method. It has been established that in a scoping study “grey literature” i.e., documents that are not formally published in academic sources such as peer-reviewed scientific studies (Farace & Frantzen, 2004) are included when extracting relevant data and refining results according to the objective and research question. Therefore, the method of scoping review was chosen for its flexibility and ability to identify key aspects or characteristics from the factors related to the concept. A literature reviews aim is to collect, evaluate and present the findings regarding a particular issue or question. (Arksey & O’Malley, 2005)

2.1 Research Questions

The objective of this study was shaped during the preliminary research portion, by using the methods of scope reviewing procedures. This method helped refine this study’s research questions. The main objectives are to answer the following questions:

1. How does artificial intelligence impact medical device regulations in the EU and the United States?
2. How does the EU medical device regulations compare to the US FDA legislation in respect to artificial intelligence in medical devices?

2.2 Data Collection Method

This scoping literature review is an academic paper which falls under the category of comparative narrative literature analysis and utilizes the methods of systematic literature reviewing process to collect relevant studies. A scoping literature review, quite similar to the systematic literature review, is conducted

as a meta-analysis by taking findings in multiple studies of the same subject and finding patterns. Choosing between these two review methods comes down to the volume and source of the research material. In this case, the subject matter is a relatively infrequently studied in academic circles with most publish material coming from organizations with no commercial or academic background. (Munn et al., 2018) However, the methods primarily used in systematic literature review are excellent tools to extract relevant material for analysing and formulating the answer to our research questions.

2.2.1 Comparison

The part of this thesis that introduces the subject matter is compromised of the narrative literature style where comparison analysis method will be used to concentrate on the “safari” approach by finding the most suitable answer to the question at hand. This method is useful when used to compare a handful or two nations and find the evidence to a well-defined question, which suits the needs of this research. (Hantrais, 2020) Comparisons have a way of leading to new and exciting insights with a deeper knowledge to issues that are a central concern in the selected countries. This deeper understanding can result in identification of gaps or may point to better roads to be taken that might not have previously been seen. Thus, the researcher can sharpen the focus of the subject and analysing it under new perspectives.

2.2.2 Scoping Research Method

Scoping studies or scoping reviews are the new frontier in reviewing health research evidence (Davis & Drey, 2009). Scoping reviews are beneficial when, "When a body of literature has not yet been comprehensively reviewed, or exhibits a large, complex, or heterogeneous nature not amenable to a more precise systematic review." (Peters et al., 2015) The method is a suitable approach to undertake when one wishes (1) to identify the types of available evidence in a given field, or (2) to identify key characteristics or factors related to a concept. (Munn et al., 2018)

According to Arksey and O'Malley there are two ways on thinking about the role or purpose of a scoping study; a gateway to producing a full systematic review or perhaps leading to one in the future. For this scoping review, the choice is to formulate a systematic review with limited scientific research data, and so fall under the first category. Table 1 introduces four different reasons on choosing the scoping study method and gives a brief explanation about the advantages.

Table 1. "What is a scoping study?", Scoping studies: towards a methodological framework (Arksey & O'Malley, 2005)

	Reason for conducting a scoping review	Advantages
1.	To assess the extent, range, or nature of the research area	When assessing the research material and its availability this type of research study might not produce many findings. It gives an estimation of the research material volume.
2.	To assess the probability of undertaking a full systematic review	An initial mapping of the literature might be undertaken to identify whether or not a full systematic review is possible. This also helps estimate the potential resources needed when conducting a full systematic review.
3.	To summarise and distribute research findings	This type of scoping study produces detailed results and variety of research. It provides a way for summarising and disseminating research findings to physicians, consultants, and consumers. (Antman et al., 1992)
4.	To identify research gaps in the existing literature	This type of study is constructed to identify gaps when a limited number of research has been conducted in the area of study. This type of study also summarises and distributes research findings, as well as assess the importance of a full systematic review.

Table 2 shows another detailed methodological framework which is based on Arksey's, and O'Malley's work. While quite similar to the systematic literature review method it also takes into consideration the potential of stumbling into a research question that does not have a reasonable number of published studies

to extract data from. Which is why the Levac et al., (2010) search strategy, shown in Table 2 below, are the main framework for this research study.

Table 2. Six-stage methodology framework by Levac et al., 2010

No.	Stage of Methodology	Description
1.	Research Question	Identifying and securing a research question for it for provides the pathway to the next stages.
2.	Relevant Studies	Identifying relevant material and limiting search to date, language, and search terms.
3.	Study Selection	Setting an inclusion and exclusion criteria post hoc (after the data has been viewed).
4.	Charting the data	A data charting form is used to extract relevant information from each study
5.	Results	Results are based on a thematic analysis which gives a broad overview of the breath of literature.
6.	Consultation (optional)	An opportunity for company stakeholders or consumer to suggest additional references and provide insider information.

Table 2 is the framework on which this thesis is built and will be periodically referred to as the scoping study progresses from the identification of the research question to identifying relevant material, implementing filters for systematic search of the three chosen databases and charting of the selected articles which lead to synthesis of result and other relevant findings. Stage 6 Consultation is optional for a scoping literature review and is disregarded in the present study due to time limitation.

2.2.3 Systematic Search

According to the Cochrane definition “A systematic literature review attempts to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question”. (Piper, 2013) Figure 1 summarizes the necessary steps to produce a comprehensive systematic literature review.

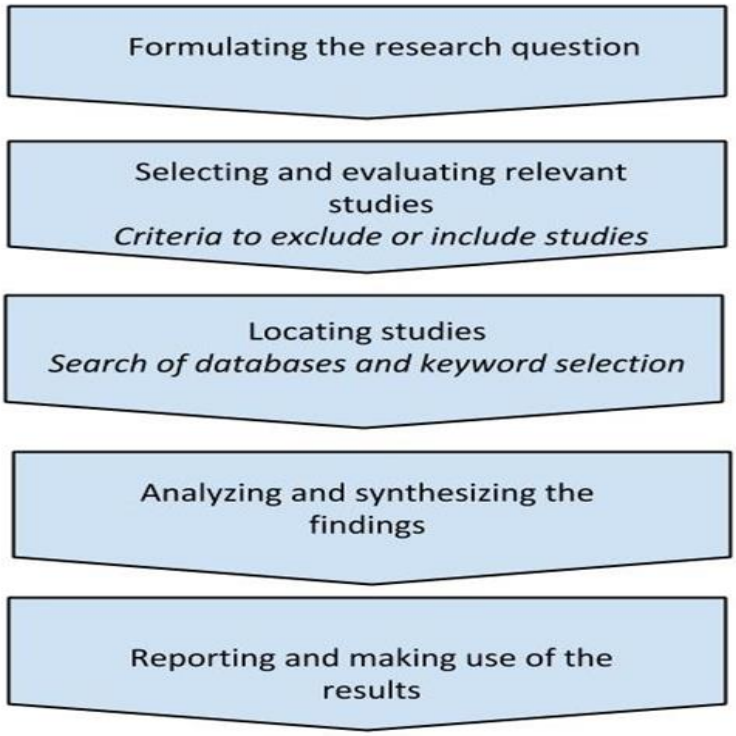

Figure 1. Research methodology for the present systematic literature review. Adapted from Denyer and Tranfield, 2009

Systematic literature review is a handy method in finding answers to questions of medical scientific nature and is used in the field of public health to investigate research topics, with the use of PICO (T) elements. This is used to find evidence-based models as a process for framing research questions. (Heneghan & Badenoch, 2008). Due to the large number of results unrelated to the research subject, search strings i.e., well thought out keywords were

required to whittle down the high volume of scientific articles found in the electronic databases.

The following elements incorporate the PICO (T) method:

- P--Patient/Problem/Population
- I--Intervention/Indicator
- C--Comparison
- O--Outcome of interest
- T--Time element or Type of Study (optional)

By shaping a question in this method, the researcher can systematically review in a rigorous and impartial way that aims to a literature-wide assessment of the study outcomes, quality, and design. (Piper, 2013) Once the main elements of the question have been identified they can be written into the sections which illustrates Problems, Interventions, Comparisons and Outcomes. (Fineout-Overholt & Johnston, 2005)

2.3 Parameters and Limitations

The limitations for this thesis and the scoping search parameters are mainly set by the scarce information available due to the newly composed EU Regulation 2017/745 that will be put into action late 2021 and will be the main reason for accumulating information involving artificial intelligence, health technology and medical device regulations from grey literature.

The study selection utilizes scientific research material which falls under the category of academic journals and review articles from three search engines that have been narrowed down due to time constraint and high-volume of materials not specifically related to the thesis subject. The limitations of a scoping review are similar to those of a systemic literature review, time and energy can lead up to a year of research work. In scoping, even more citations are screened than otherwise, with different screening/process than systematic

review which then often leads to a broader and less defined search. The study strategy can also lead to more than one search and increase emphasis for hand searching the literature which is why some scoping studies might require a larger teams or workers due to the volume of subject related literature.

The part where collected studies are critically appraised as according to Table 1 “Six-stage methodology framework by Levac et al.,” is Stage 4. Charting the data, instructs the researcher to use a critical appraisal instrument. This critical appraisal form of the data selected is usually validated by another evaluator. In this thesis the critical appraisal is done by the author based upon its suitability to answer the research questions at hand. There is a risk of inconsistency in when conducting a scoping study due to its nature of being a precursor to a more replicable systematic review.

In conclusion, documents pertaining to the USA and European governing bodies and their regulatory affairs; FDAs’ Medical Device Regulations and the EU Regulation 2017/745 are reviewed and analysed. This includes documents and other written or visual material regarding artificial intelligence in medical devices regulations; its usage, benefit, limitations, risks etc. are also taken into consideration when browsing through grey literature.

3 Medical Device Regulations and Standardizations

Medical devices have an inherit probability of hazards and can be classified from simple, low-risk devices such as stethoscopes to complex, high-risk devices such as pacemakers which contain embedded software. (Rome, Kramer et al., 2014) Because of these inherit hazards that may put consumer and/or patients’ lives at risk, governing institutes across nations have acted by implementing laws that made sure that medical devices accessible by consumers are being protected. The largest medical device regulators around the world can be found in Figure 2. These global regulatory authorities recognize the devices based on the complexity of the device and classifies it according to its intended use.

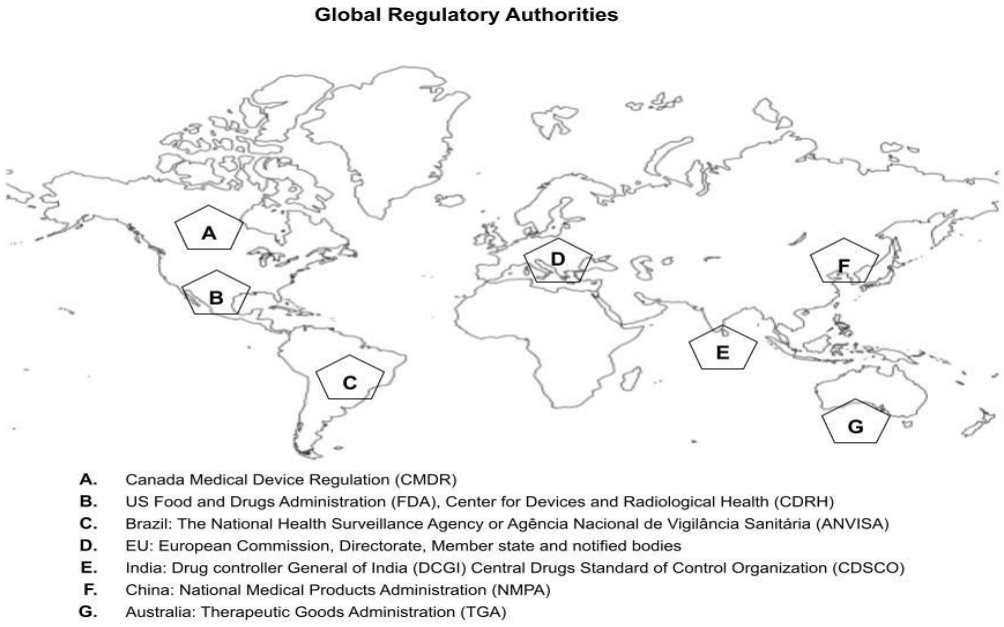

Figure 2. Global regulatory authorities. Authors own work. Adapted from Ramakrishna, Tian, et al., (2015)

The regulation of medical devices is a vast and rapidly evolving field. The Global Harmonization Task Force (GHTF) now called the International Medical Device Regulators Forum (IMDRF) proposes a comprehensive medical device classification in order to harmonize and unify risk management by proportionating its potential hazards to its degree of regulation. The goal is to maximize benefit and minimize risk in medical devices. Medical device safety and risk management cannot be solved until extensive market experience has been gained, for safety can only be considered in relative terms. (IMDRF, 2021)

According to WHO Medical Device Regulations manual, the optimum assurance of medical device safety has several essential elements which are summarized in the list below. Each of these features must be taken into consideration when outlining guidelines for medical device safety as the goal is to always minimize risk and maximize benefit. (WHO, 2003)

Features that are relevant to the assurance of medical device safety are as follows:

- Risk management and device classification

  The International Organization for Standardization (ISO) has published ISO 14971:2000 which builds a framework for risk management; risk analysis, risk evaluation and risk control. Risk assessment can be categorized into device classifications based on potential areas of perceived hazard.

- Device effectiveness/performance

  MD device effectiveness must be based on strong scientific background to prove clinical efficiency. Performance is closely related to safety and the inherent risk of a medical device. Regulatory authorities require manufacturers to implement risk management process to meet performance and safety guidelines.

- The responsibility of stakeholders

  Stakeholders in this context include manufacturers, users, vendors, the government, and the public/patient. While the first three participants are directly involved with the product, the last two also play key roles due to their beneficiary and responsibility in the medical device. For example, the manufacturers work does not end with the purchase of the medical device. Post-market surveillance is necessary to ensure that the medical device is up to task when conducting inspections and monitoring of adverse effects. The responsibility of continued safety of medical devices lies with all five of the stakeholders. With cooperation and common understanding of the issue safety and performance can be ensured.

- Life span of a medical device

  In truth the phases may overlap and interact during design, development, and clinical trials, but they are simplified to understand regulatory processing.

Figure 3 showcases in a simplified manner the lifecycle of a medical device from conception to disposal.

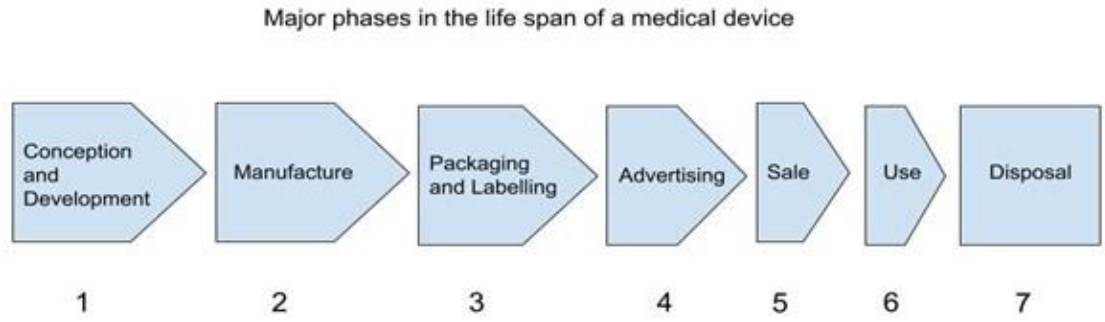

Figure 3. Lifecycle of a medical device. Adapted from WHO manual of Medical Device Regulations; Global overview and guiding principles, 2003

The lifecycle of a MD is listed and expanded upon in each numbered (1-7) phases in the text below. Each phases includes multiple steps and is pertinent to the device lifespan as showcased in Figure 3.

1 Conception and Development

Investigating the concept of a new medical device and developing a prototype are part of the first phase which lead to validating a concept. The working prototype must overcome regulatory hurdles which vary based on device class. Device classifications are based on risk, invasiveness, and purpose. For example, the USA Food and Drugs Administration has three classes from one to three. Whether clinical trials are necessary depends on the MD. Pre-Market approval is submitted to the regulatory authorities after all trials and testing have been concluded.

2 Manufacture

To maintain high quality and remove any inconsistencies in manufacturing of the products, Good Manufacturing Practice (GMP) must be upheld. GMP or most commonly known as Quality Manufacturing Systems (QMS) is addressed later in the chapter.

3 Packaging and Labelling

Medical device packaging must be done properly, even when the product might be sterile and potentially biohazardous. The risk to handling of such devices must be minimal and the packaging systems should be design with these requirements in mind. The packaging systems must also take into consideration of shipping issues such as subtle damage during transportation. Labelling is necessary to identify the device and instruct the user of proper use. This will minimize serious consequences such as risks, malpractices, and accidents.

4 Advertising

Manufacturing can start when given the Pre-market approval letter. It gives the manufacturers a green light to produce more devices as long as they ensure materials meet regulations and advertisement is not misleading or fraudulent by working closely with a legal team.

5 Sale

According to WHO the sale of the device from vendor (importer, distributor, seller) to buyer is critical for it allows a higher risk of ineffective devices reaching the market. It is crucial that the vendor be subjected to proper regulations because it will decrease the chances of low-quality medical devices reaching the user.

6 Use

The users of medical devices must know proper care and procedures to ensure their and the patient’s own safety. Performing contrary to manufacturer’s instructions can lead to serious consequences to their safety and health.

7 Disposal

To ensure safety, it is necessary for the disposal of certain medical devices to follow stringent protocols and rules when disposing of contaminated or hazardous parts. This ensures that the people involved in the disposal process and the environment are protected from any form of harm.

The WHO has outlined in the World Health Assembly (WHA) that it mandates every member state to develop national or regional guidelines for good manufacturing and regulatory practices which will ensure quality, safety, and efficiency in medical devices, and if possible, to participate in international harmonization standardization. (WHA, 2007)

3.1 Standards for Medical Devices

The standards for medical devices are written by International Organization for Standardization (ISO) or International Electrotechnical Commission (IEC). The ISO give the following as a formal definition of a standard in regard to medical devices; standards contain specific technical requirements or precise criteria which need to be obtained to ensure materials, products, processes, services, systems, or persons are fit for their intended purposes. Standards in general are not considered to be best practices or even be “state of research”, but to prove the “state of the art”. They are published under the authority of experts in their respective fields and have no governing authority. The international standard body is composed of representatives from national standardization organizations. These standards are developed in different levels.

For example:

- National: American National Standards Institute (ANSI),
- Regional: European Committee for Standardization (CEN),
- International: International Organization for Standardization (ISO)

Most standards contain a specification type such as management specifications which set out quality systems for manufacturing (ISO 9000) or environmental

management systems (ISO 14000). Medical device manufacturing specific quality systems standards can be found in ISO 13485 and ISO 13488. These documented standards are minimum requirements that need to be fulfilled by the professional company, business, or organization. With the world connected more than ever, it needs and benefits from common standardization. Having a harmonized medical device standard is necessary when the same device is being sold globally.

3.1.1 ISO 9001

Harmonized standards such as ISO 9001 have been identified by the European Union in the Official Journal. By meeting these standards, it is presumed by auditors that, manufacturers have met the requirements in EU medical device regulations. Those notified by the CEN are proven to be in compliance with EU regulations. The 9001 standard is the International Standard for Quality Management Systems (QMS) from the family of ISO 9000, and defines the criteria for development, implementation, and effectiveness. It is the general standard for quality management and is not industry specific. The influence of ISO 9001 on medical devices is broad ranging for it completely effects all companies that design and manufacture medical devices. For medical device manufacturers this standard engages management in the quality control process by keeping manufacturing costs low and improving accountability.

3.1.2 ISO 13485 and ISO 14971

Medical device manufacturers that manufacture medical devices according to this standard are expected to follow the standalone ISO 13485 for it has additional requirements. It refines and expands on the framework established by ISO 9001. The medical device standard sector falls under the guidelines and requirements of ISO 13485, Medical devices — Quality management systems — Requirements, and is accepted by the EU and FDA.

Absolute safety cannot be guaranteed since it is closely tied with the phases of the medical device's life span. Risk is measured by identifying possible hazards and estimating each of them. From conception to usage, a risk assessment must be composed. Risk management process and documentation for medical devices is compulsory when seeking regulatory approval. The U.S., Canada, EU, and Australia TGA all endorse ISO 14971 Medical devices -- Application of Risk Management to Medical Devices.

Risk management also includes technical standards such as IEC 60601 which contributes to safety and essential performance of electrical medical devices, and IEC 62366 a standard that specifies usability requirements. While the Risk Management Policy is focused on the company's quality management system the Risk Management Plan is a product level document which identifies the risks anticipated and planned during the medical devices lifecycle. This ISO standard is in compliance with ISO 13485 which is the norm to understand and guide the company with its plan to measure and evaluate risks. It is important that the medical device manufacturing company's top management is involved when building the Risk Management Policy that consists of the following process as listed in Table 3 below.

Table 3. Risk Management Policy implementation

No.	Phase	Implementation
1.	Establishment of Risk Management Framework	The risk management process and establishing management roles and responsibilities withing the company.
2.	Risk Analysis	Risk analysis and assessment consists of specifying the intended use of the device, identifying potential hazards, defining this potential source of harm, and making an assumption of sequences of events that lead to it.
3.	Risk Evaluation	When the risks have been determined, it is required to estimate and evaluate the levels of risk by utilizing a risk accessibility matrix. Most commonly

		charts measure the probability and severity of each scenario, and which help determine if a Benefit Risk Analysis is needed.
4.	Risk Control	Risk control process contributes to the process of making decisions and measuring the implemented risks which need to be reduces or maintained within its specific risk levels. Risk Control options are chosen based on the nature and location of the risk.
5.	Overall Residual Risk Acceptability	After evaluating residual risks and complementing Risk/Benefit Analysis the evaluation of overall residual risk acceptability makes it possible to see if the benefits outweigh the potential of risks.
6.	Risk Management Review	Performing a risk management review and building a risk management report the company can confidently send out its medical device for commercial production.
7.	Production and Post-Production Information	Surveillance of market including customer feedback or complaints, internal audits and all post-production information is put back into the risk management process.

The RMP is integral to medical device manufacturers as the harmonized standard ISO 14971 requires all medical devices include a defined risk policy with the correct method of risk assessment taken and that all risks must be assessed according to the risk policy.

4 Medical Device Regulatory EU and US

One of the reasons for a cross-nationals comparison is the concentration of medical device companies and where the subsequent organizations are located. This is based on the latest information regarding the manufacturing of medical devices, where the United States dominates with a market value of 169 billion USD. (Fortune Business Insights, 2021) The European medical

technology market follows second with a significantly lower share of 140 billion EUR. (MTE, 2021)

4.1 Definition of Medical Device

When defining the definition of a medical device (MD) the EU has decided that a medical device can mean any instrument, apparatus, appliance, software, implant, reagent, material, or other such object intended by the manufacturer to be used, alone or in combination for human beings. (Medical Device Regulation (EU) 2017/745). The full definition can be found in Article 2(1) of the MDR.

The United States Food, Drug and Cosmetics Act in Section (201) h also uphold similar traits when defining the characteristics of a medical device:

> “An instrument, apparatus, implement, machine, contrivance, implant, in vitro re-agent, or other similar or related article, including a component part, or accessory which is:
>
> 1. recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
>
> 2. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
>
> 3. intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and…
>
> which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o).” (FDA – Section (201) h)

Since a large range of devices fall under the category of being a medical device or health application, the following document is thus limited to medical devices only and will be excluding in vitro devices (IVD). These devices have a separate

regulation in the new European Union Regulation (EU) 2017/746. The definition of an IVD Medical Device is defined in the IVDR as any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body. (Medical Device Regulation (EU) 2017/746) The full definition can be found in Article 2(2) of the MDR.

To summarize, medical devices are healthcare equipment or products that are used for medical purposes and have at minimum a partial role in patientcare. These vast coverages of apparatus come as bandages to implants, benefit patients by treating illnesses, whether acute or chronic and improving their quality of life. The devices also support healthcare professionals monitor, diagnose, assist, and improve patient treatment.

4.2 FDA Regulatory Approval

In the United States, the first legislation concerning medical devices was signed by the then President Franklin Roosevelt in 1938. (FDA, 2018) In modern times the federal agency regulates and supervises items such as food, pharmaceutical drugs (including vaccines) and cosmetics. They also regulate medical devices and veterinary products. The FDA was given the task of regulating all medical devices on May 28th, 1974, when the President in office, signed the Medical Device Amendments Act. The FDA proposes, reviews, modifies, and revises which are finally placed in the Code of Federal Regulations (CFR), Title 21, Parts 800-1299. (Sutton, 2019) Within the FDA is the Center for Devices and Radiological Health (CDRH), which looks after all medical devices and ensures that there is minimal exposure from radiation-emitting MD’s. The Medical Device Product Classification database lists over 6000 types of MD’s and all of them are regulated by the CDRH. (FDA, 2020)

The FDA categorizes the medical devices into three classes (Class I, Class II, Class III). For example, Class I products can be support medical stockings, with the intended use for general medical purposes in general hospitals, are exempt from the pre-market notification 510(k) marketing pathway. (Sutton, 2019) When class category has been applied to the finished product they also require to be subjected to general controls. General controls in this case mean that all MD manufacturers must comply with quality system regulations. For general control requires that all medical devices be properly labelled. Another factor of general controls is reporting which the manufacturers, importers and user facilities must do in case of device malfunction to the Medical Device Reporting program.

The regulatory framework which all MD manufacturers use is 'Title 21-CRF Quality Systems Regulations'. By estimating the device risk factors, manufacturers identify the correct marketing pathways. Manufacturers must also list their device(s) into the electronic establishment register with the FDA by the time they plan to market the product. The list below are FDA marketing pathways for medical devices.

1 Premarket Notification 510(k) is a clearance process that demonstrates that the device in question is noticeably similar to another legally qualified device on the market. The FDA determines if a device is Substantially Equivalent (SE) to a legally marketed device (predicate device) that is not subjected to Premarket Approval (PMA).

2 Special 510(k) approval pathway can be requested when the device in question has been modified or will be modified. By submitting a Conformance to Design Control to quality systems regulation, the applicant can have the approval process speeded to 30 days from the traditional 510(k) and Abbreviated 510(k) timeline-processing of 90 days.

3 Abbreviated 510(k) approval pathway is submitted when the applicant is complying with a guidance or standard. The data reviewing process lasts the estimated 90 days.

4 Exempt means that a Class I MD does not require a 510 (k) clearance, for example devices without a measuring function and are not sterilized. The regulation in CFR will state whether a device is exempt or not.

5 De Novo Classification Request is sent to the FDA when 510 (k) marketing pathway classified devices (Class I and Class II) general or special control

is applicable, but it has no legally marketed predicate device and is Not Substantially Equivalent (NSE).

6 Premarket Approval (PMA) is for devices that are high-risk and may be used as life-supporting/sustaining MD's or they can be completely new with no SE. The main purpose of PMA application process is to prove through a scientific, regulatory documentation that the device safety and effectiveness is sound. Most PMA's contain large volume of data from clinical and non-clinical studies, manufacturing methods, and other technical information.

7 Product Development Protocol (PDP) is a modular approach to the traditional PMA. It is for devices that are well established in the industry for clinical evaluation of the device and necessary information of development are combined into one regulatory mechanism.

8 Humanitarian Use Exemption (HDE) takes into consideration rare diseases. Rare diseases are defined as a disease or condition that affects less than 200 000 people in the United States of America. The sufficient amount of data from clinical trials which are needed is difficult to achieve when the affected individuals consist of a small portion of the population and makes it nearly impossible to gather enough evidence for the stringent FDA clinical evaluation. This would be a challenging hurdle to overcome without an exemption to the regular pathways.

These marketing pathways are regularly used as means to get the product into the consumer market as fast as possible.

4.3 EU Regulatory Approval

For countries that are members of the European Union (EU), the safety and performance of medical devices were harmonized in the late 90's. The rules defined by the *New Approach* in the European Council Resolution (Council Resolution of 7 May 1985 on a new approach to technical harmonization and standards, 1985); the core legal framework consists of the three following directives:

1 Directive 90/385/EEC regarding active implantable medical devices

2 Directive 93/42/EEC regarding medical devices

3 Directive 98/79/EC regarding in vitro diagnostic medical devices (Until 2022, the In Vitro Diagnosis Regulation (IVDR) will replace the EU's current Directive on In-Vitro Diagnostic (98/79/EC))

The EU which regulates medical devices for human use repealed the former Council Directives 90/385/EEC and 93/42/EEC, and amending Directive 2001/83/EC, Regulation (EC) No. 178/2002 and Regulation (EC) No. 1223/2009 on the 5th of April 2017. (EU, 2017)

The new Regulation (EU) 2017/745 which was agreed upon at a political level between the three European institutions; the European Council, the European Parliament, and the European Commission, was published on 5th of May 2017, in the Official Journal of European Union and came into force the following month. The date, originally given for the transition time of three years, was 26th of May 2020, but was postponed due to the international health emergency of COVID-19. The new timeline has been extended by one year to 26th of May 2021. The new legislation is now a Regulation, instead of a Directive, meaning the new law is applicable at a national level. This should reduce variations on MD legislation between EU Member states and lead to more unity in standards when approaching medical devices.

The changes to the previous Medical Device Directive which had been in place for over 25 years include a new subclass for Class I, the creation of the European Union database for medical devices (EUDAMED) registry and its registration, increase of post-market surveillance, the requirement of a unique device identifier (UDI), and more strict oversight of manufacturers by the Notified Bodies. The scope and classifications of devices have broadened to include products without an intended medical purpose such as cosmetic laser removals, contact lenses and others. This change also includes a new category of Class I r for reusable surgical instruments. Another change included in Regulation (EU) 2017/745 is the economic operator roles (Manufacturer, Authorized Representative, Importer and Distributer).

In the EU the manufacturer is responsible for choosing the correct regulatory pathway for a CE mark. "CE" is the abbreviation of "Conformité Européenne" (French for "European conformity"). To place a medical device in the EU market it must meet all requirements and applicable EU directives i.e., completing a

conformity assessment procedure. For commercial products that behold the CE mark, indicate that the manufacturer affirms the products conformity with European health, safety, and environmental protection standards. It also indicates that the product may be sold in the European Economic Area (EEA) but is not a quality indicator or a certification mark.

Through risk classification of the product in question the manufacturer must carry out a conformity assessment or the Notified Body must carry out tasks related to the assessment procedures. Manufacturers of the devices of all four risk classes must compile a device Technical Documentation and evidence of Quality Management System, as outlined in the Essential Requirements. Only self-declared devices falling into Class I (and excluding products in I lm, Is, Ir) can be done without the involvement of a Notified Body once the manufacturer has evidence of conformity with the relevant General Safety & Performance Requirements (GSPR).

5 Medical Device Classification and Software as Medical Device

As a manufacturer it is pertinent to understand that the definition of medical device is related to its intended use. Knowing what the product usage, purpose and action is, will result in correctly classifying the MD product.

5.1 MD Classification

In the US, according to the FDA; medical device classifications are assigned by based on the level of control necessary to assure the safety and performance of the device in other words they are based on the risk of the device. The controls in question are implemented according to the device classification. There are in total three categories with requirements which apply to them.

- Class I and II: Low and moderate-risk devices, such as a stethoscope, pregnancy kits or a computed topography (CT)

scanner, fall under the 510(k) regulatory approval, marketing pathway.

- Class III: High risk devices, such as pacemakers or deep-brain stimulators require a process of scientific and regulatory review; a Pre-Market Approval (PMA) with demonstrated data, validation of safety and performance, and a comprehensive risk/benefit analysis assessment of the medical device.

Like its USA counterpart, the EU MDR it is also constructed of a risk-based classification. The European Union MDR categorizes its devices according to four different classifications: I, II and III.

- Class I: Non-invasive and low-risk apparatuses with non-sterile or no measuring function, such as simple bandage or otoscope. Equipment such as these do not need to be involved with a Notified Body and can be self-declared.
- Class Im, Is, Ir: Non-invasive, low-risk sterile and measuring devices, and reusable surgical instruments must be reviewed by a Notified Body that review aspects related to the device's conformity, securing, maintenance etc.
- Class IIa: Medium risk devices are those which are installed within the body from 60 min to 30 days such as hearing aids and blood testing tubes. The requirements for such devices include technical files and conformity test done by the Notified Body.
- Class IIb: Medium-high risk devices are mostly invasive or active devises which are partially or completely implanted into the human body. Devices that fall into this category are intensive care patient monitoring medical devices and have an added requirement of device type examination by NB.
- Class III: High risk medical devices that require full quality assurance system audit, examination of MD design and development by the EU NB. Devices that are high risk include pacemakers and balloon catheters.

There are 22 rules when categorizing non-invasive, invasive, active devices and special devices. The classification is based on risk and is set out in Annex VIII, where software can be an active device, a standalone software (SaMD) or a combination incorporated with other devices. This means that the MDR includes mobile apps with healthcare features.

5.2 Software as MD

Due to ever evolving high-end technological achievements, software is integrated into various medical devices. The International Medical Device Regulators Forum (IMDRF) has defined Software as a Medical Device (SaMD) as "…software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device." (IMDRF, 2013) The European Commission's Medical Device Coordination Group (MDCG) has named it Medical Device Software (MDSW) and defines it as "…software that is intended to be used, alone or in combination, for a purpose as specified in the definition of a "medical device" in the medical devices regulation or in vitro diagnostic medical devices regulation." (MDCG, 2019)

Global approach to the medical software market varies on the device type, application, deployment type and geography. It has been estimated that in the next six years market forecast for SaMD will increase from almost $19 billion in 2019 to almost $87 billion in 2027. The Compound Annual Growth Rate (CAGR) is estimated to increase 22 % in this timeline. The main reason for this growth is due to Internet of Things (IoT) and other devices in the healthcare sector. (Insight Partners, 2020) Applications of IoT in the medical field have been further invested in due to advantages with integration of medical software development. Such development can be applied to continuous monitoring of physiological activities and collection of patient data for those suffering of choric illnesses.

5.3 EU Classification of MDSW

Qualifying software as a medical device under EU regulations means manufacturers must fulfil the following definitions of "medical device", "software", or in vitro diagnostic medical device according to Article 2(1) of Regulation (EU) 2017/745. This must be done regardless of whether the software is independent or driving or influencing the use of a device.

Besides the intended use, most software in medical devices classify, according to MDR as class IIa or higher due to Rule 11 of Annex VII of Regulation (EU) 2017/745. In case of Rule 11 the sub-rules state that anything which does not provide data on which is utilized to make decisions for diagnostic or therapeutic purposes, or does not monitor physiological indicators or parameters, implies that all other MDSW fall under class I. Before the rule was compiled, most software medical device applications fell under class I category. The reason behind this is the added Rule 3.3. of Annex VIII which determines that software driving or influencing the use of the device; ‘Software, which drives or influences the use of a device, shall fall within the same class as the device’, is implemented when considering an independent MDSW; ‘If software is independent of any other device, it shall be classified in its own right’. Further implementing of Rule 3.5 Annex VIII states that all devices which fall under several rules or several sub-rules, the strictest rule or sub-rule will categorize it as the one with the higher classification. (MDCG, 2019)

The illustration below (Figure 4) is adapted and simplified from the Medical Device Coordination Group document, “Annex III - Usability of the IMDRF risk classification framework in the context of the MDR”, which showcases medical device software that are scored with a higher class than Class I. The healthcare scenarios, which collect or detect data from the software, are vital and help determine patient management depending on the patient condition. By rating the seriousness of the condition, MDSW will be classified according to the Rule 11 Classification Guidance.

		Importance of the data collected through the MDSW		
Healthcare situation or patient condition		High	Medium	Low
	Critical Condition	Class III	Class IIb	Class IIa
	Serious Condition	Class IIb	Class IIa	Class IIa
	Non-threatening	Class IIa	Class IIa	Class IIa

Figure 4. Rule 11 Classification Guidance according to MDCG. Adapted from the MDCG Document; Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR, 2019

It is important to remember that the MDSW applies to the software-only devices and hardware devices that include MDSW as a vital part. This is for example an infusion pump which includes an insulin dose calculator to achieve the necessary action.

5.4 US Classification of SaMD

The United States of America approaches the regulation of software as a medical device (SaMD) by considering its intended use and whether it is part of an in vitro medical device. There are three types of software involvement with medical devices and the one where Software as a Medical Device, meaning Software which as its own is a medical device, gets the classification of SaMD. The other two types are software in a medical device, meaning it is integral to the function of the medical device and software used in a manufacturing or maintenance of the medical device. (FDA, 2018)

In 2013, chaired by the FDA the International Medical Device Regulators Forum (IMDRF), which consist of MDR experts from across the globe formed a workshop; the Software as a Medical Device Working Group (WG) which then built a set of guidelines for risk categorization, Quality Management Systems, and clinical evaluation of Software as A Medical Device (SaMD).

The document ‘Software as a Medical Device (SAMD): Clinical Evaluation - Guidance for Industry and Food and Drug Administration Staff’ declares the SaMD manufacturer responsibilities on classifying it accordingly. Figure 5 illustrates that by defining its intended use according to the key definitions, the manufacturer can use the below “table” as guidance on deciding the right class.

		Importance of the data collected through the SaMD		
Healthcare situation or patient condition		Treat or diagnose	Drive Clinical Management	Inform Clinical Management
	Critical Condition	IV	III	II
	Serious	III	II	I
	Non-threatening	II	I	I

Figure 5. SaMD Categories. Adapted from IMDRF SaMD WG N12/ "Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations, 2014

The framework of this illustration (Figure 5) is based on the documents ‘IMDRF SaMD WG N12/ "Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations’, which has set the criteria’s for determining the SaMD category with I being the lowest and IV having the highest impact when implementing SaMD data collected diagnoses or therapeutic processes, and ‘IMDRF SaMD WG N10/Software as a Medical Device: Key Definitions’, which concentrates on a common definition for when software is considered to be a medical device and a list of other key terms, some which have already been defined in Global Harmonization Task Force (GHTF) documents, in application to SaMD.

6 Artificial Intelligence

The concept of intelligence can be traced back to the Latin nouns intelligentia or intellēctus, which in turn stem from the verb intelligere, to comprehend or perceive. However, defining intelligence is more controversial as psychologists are still debating which elements constitute intelligence. While the definition can vary from theorist to theorist, there are certain aspects that have been widely recognized as conceptualizing intelligence; the ability to learn from experience, recognize and solve problems. (Jaarsveld S and Lachmann T, 2017)

The meaning of artificial intelligence for the general public is steeped into what is seen in popular culture and its various artforms. For many, the monotonic voices with a hint of personality, is what comes to mind when the concept of AI is mentioned, but for the scientific community artificial intelligence, sometimes called machine intelligence, is founded on the Turing Test, where computer mathematician Alan Turing asks a simple question: “Can machines think?” (Graham and Dowe, 2020) Broadly defined, machines that have intelligence and are capable of learning from their mistakes are classified as having artificial intelligence. But what is intelligence and which characteristics must be given to presume a subject or an object as intelligent?

There is no textbook answer, though the authors of *Artificial Intelligence: A Modern Approach*, Stuart J. Russell and Peter Norvig, approach the question and give the following answer: *"the study of agents that receive precepts from the environment and perform actions."* (Russell and Norvig, 1995) Answers such as these might seem abstract to a non-expert, but in science it brings focus, and gives a more substantial blueprint for those in the field of computer science.

6.1 AI Development

Artificial intelligence (AI) was confined to the world of science fiction for centuries. It was only in the mid-50’s that the term “artificial intelligence” was first proposed by an American computer scientist named John McCarthy and was coined into existence. (McCarthy, 1988)

In 1983, Elaine Rich defined AI as a subarea of informatics; “the study of how to make computers do things at which, at the moment, people are better.” (Rich and Knight, 1991) But the actual timeline for AI begins at a simple workshop in Dartmouth College, in the year of 1956, where the pioneers of modern computer science gathered, and in many ways, founded it as an academic discipline. (Kaplan, Haenlein, 2019). The conference at Dartmouth College led to a time period between 1952 and 1969 of early enthusiasm and high

expectations. It was during the first half of this period that Allen Newell and Hebert Simon wrote a set of problem-solving computer simulation program The Logical Theorist which was the first successful AI system in history. The program simulated the thought process of a person to prove the symbolic logic theorem and correctly proves some mathematical theorems. (Dick, 2013)

In 1958, John McCarthy, one of the participants in the 1956 summer workshop and the person to first propose the term artificial intelligence formally, developed the programming language LISP. This was an important contribution to AI development for it became the predominant programming language of AI for the next 30 so years. By the mid-70's the academic interest towards AI technology slowed down and led to a period called *the AI winter*, a term for the bouts of years between where no development or research were being done. (Crevier, 1993) The consequent period of "winter" continued until 1982 when the Japanese government for its Fifth-Generation Computer Systems (FGCS) project, launched what many called was a visionary initiative, poured funding and recourses into what they thought was the future of technology. (Feigenbaum, Shrobe, 1992) This lit the fire for many nations and industries to contribute to the improvement and newfound knowledge of AI in the academic field during the 80's.

The ten-year project plan to build an intelligent computer with a programming language named PROLOG, which at the time was less common than LISP ended up being a mistake for it led the demise of the Fifth-Generation project. Unfortunately, it was not long after that in 1980's another "AI winter" descended upon the field and restricted any progress being made. (AI100, 2016)

For the last couple of decades there have been a lot of advances in AI and its applications. By the 1990's scientist focused on research of artificial intelligence related to real-world issues such as medical diagnoses and healthcare. The famously known IBM project Deep Blue in 1997 was able to defeat the world chess champion Garry Kasparov. (IBM, 1997) The research produced by IBM has made it possible for computers to tackle complex problems in fields other

than computer science. In the early 2000's Honda, the Japanese automobile manufacturer took the stage by developing a humanoid two-legged robot. This walking bot named ASIMO was created to be a sociable companion to humans and to serve as a partner. And with more time came more innovation as a team of MIT engineers build Kismet, a robot capable of actually socially interacting with people and performing facial expressions. Withing this same period autonomous understanding of text was refined, and new achievement acquired for machine reading development.

In 2010, the first AI personal assistant, Apple's Siri was introduced to the world. The ability to bring forth an independent machine that can continuously learn better than any human and improve any faults has not yet been fully achieved. But studies show that, at certain medical practices, AI is at a same level or even better in comparison to healthcare professionals. (Davenport & Kalakota, 2019) The improvement of AI has been significant and for future generations it is a reachable goal for humanity, especially, when you contemplate the progress of algorithms which can beat a chess master and diagnose breast cancer better than doctors. (Soltis, 2019) (Rodriguez-Ruiz et al., 2019)

6.2 AI Characteristics

Elaine Riches study on how to automate human intelligent behaviour provides a good outline on the underlying content of AI. The characteristics of a system with AI is as follows:

- Processing of natural language to communicate comprehensively,
- Sufficient storage of data,
- Automatic logical reasoning in responding to environmental stimuli,
- Capability to learn from readjustment of reactions (Russel & Norvig, 2011, p.23)

These characteristics are also analysed by the famous mathematician and codebreaker, Alan Turning who developed the Turing test, an intelligence test for machines in 1950.

6.2.1 Turing Test

In his seminal paper, “Computing Machinery and Intelligence”, which was published in 1950, Alan Turing introduced the idea of the Turing Test to the general populace. (Turing, 1950) The Turing Test is also known as the Imitation Game and is illustrated in Figure 6. It considered the question on whether machines could think and was a proposal to answer this that led to the creation of the Imitation Game. (Oppy and Dowe, 2020)

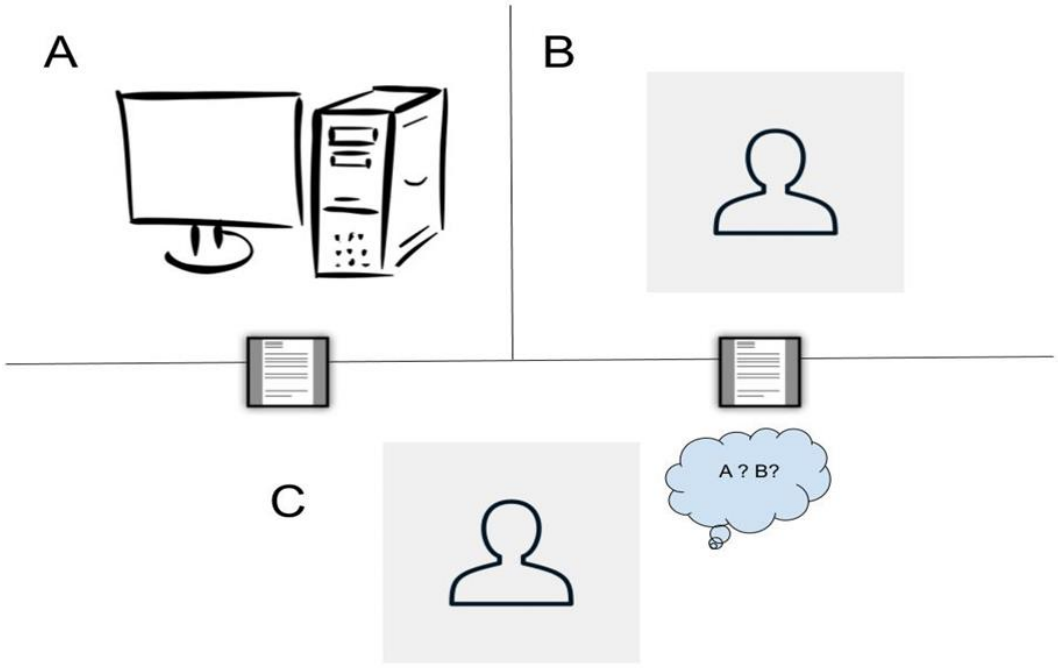

Figure 6. Representation of the Turing test. Authors own work.

In the Imitation Game, a digital computer (A) and a person (B) need to have a five-minute-long conversation with a third party(C). The third party in this case is the interrogator who asks question to distinguish between the computer and the human. The computer passes the test if it can convince the interrogator in 30 percent of the cases. (Russel & Norvig, 2011, p.1177) About this game, Turing (1950) says:

> “I believe that in about fifty years’ time it will be possible to programme computers, with a storage capacity of about 10^9, to

> make them play the imitation game so well that an average interrogator will not have more than 70 percent chance of making the right identification after five minutes of questioning. … I believe that at the end of the century the use of words and general educated opinion will have altered so much that one will be able to speak of machines thinking without expecting to be contradicted."

The first program claimed to have passed this test was a computer program named Eugene Goostman which simulates a 13-year-old Ukrainian boy. On June 7th, 2014, Eugene convinced 33 percent of the judges that it was human. (University of Reading, 2014)

The expression, "The Turing Test", is also used to refer to certain type of behavioural tests to determine intelligence and thought in entities. During the last 50 or so years there has been multiple objections to this test and the most commonly referenced one is Seales's thought experiment "The Chinese Room". In "Minds, brains, and program, John Searle argued against Turing's claims that, "appropriately programmed computers literally have cognitive states". (Searle, 1980) The Chinese Room argument denies the notion that a digital computer executing its program can prove to have a consciousness. (Harnad, 2001)

6.2.2 AI: Weak and Strong

Another characteristic of AI is differentiating between the weak and strong AI systems. Strong AI, also known as general AI or artificial general intelligence (AGI) is a form of AI used to summarize a certain mindset of AI development. (IBM Cloud Education, 2020) This theoretical form is used to describe the kind of artificial intelligence that is self-aware and capable of human like behaviour with a similar intelligence. (Fjelland, 2020) It can solve problems, learn, and predict future obstacles. Consequently, weak AI also known as narrow AI is only capable of performing a simple task and only one of them. Unlike strong AI it not capable of performing two at the same time. A weak AI can only do its task under the guidance of humans and needs subsequent interference to complete its duty. Examples of weak AI are self-driving cars and virtual assistants. (al-

Rifaie & Bishop, 2012) Table 4 summarizes the defining characteristics of “Strong AI” and “Weak AI”.

Table 4. Differences between Strong AI and Weak AI

Weak AI applications	Strong AI applications
No imitation and only capable with human interference	Can think and carry out actions of their own i.e., imitation of human behaviour
Pre-programmed by humans	Complex algorithms that lead to developing behaviour
Technologically achievable	Technologically not advanced enough

While there are no Strong AI that come close to being realized the field of AI is full of innovation and progress. This trend is seen in the following fields:

- Behavioural recognition and prediction: Job recruiting, weather forecast and stock markets,
- Entertainment and content creation: Poetry, music, video games and art,
- Cybersecurity: Firewall breaches, risk analysis etc.

Weak AI is seen in virtual assistants such as Amazons Alexa and Apples Siri, which use voice recognition, interpretation and give programmed responses. They classify words accordingly and give information that simulate human-like experience. (Kerns, 2017)

6.3 Machine Learning

The field of medical and health technology is being transformed by the use of algorithms that lay the groundwork of machine learning (ML). A subset of artificial intelligence concerned with the implementation of computer software that can learn autonomously quickly and efficiently, which lead to diagnosing, screening, and enabling better prevention of diseases.

There are various types of artificial intelligence, and it has numerous techniques. Deep learning is part of a broader family of ML methods as illustrated below (Figure 7). For example, cancer researchers use deep learning to automatically detect cancer cells. (Rodriguez-Ruiz et al., 2019) Figure 7 shows how Machine Learning and Deep Learning fit into AI technology.

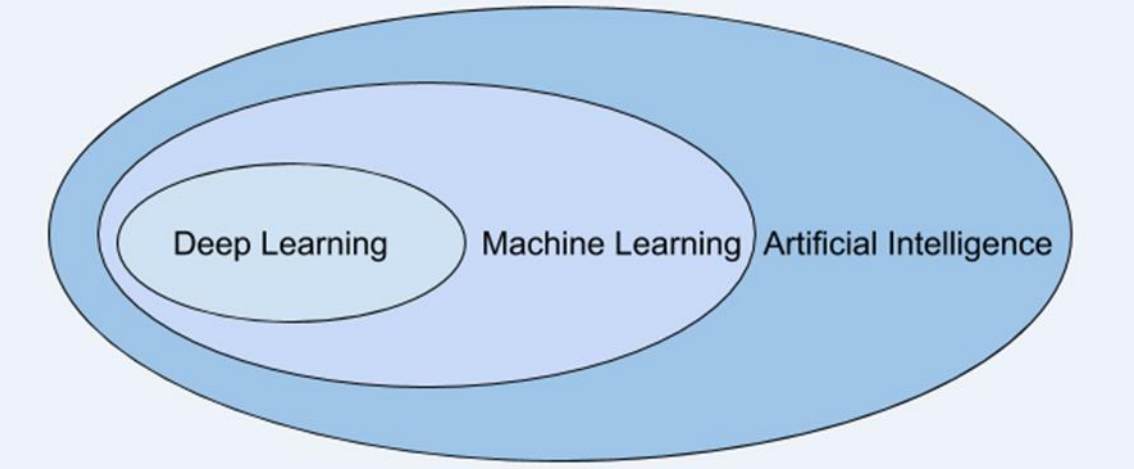

Figure 7. AI and sub-disciplines. Adapted from Goodfellow et al., (2016)

The deep learning method works by learning and developing artificial neural networks (ANNs) from gathered data i.e., Big Data (an enormous amount of data accessed from different platforms such as social media, internet search engines, online databases etc.), and recognizing patterns for use in decision making. Artificial neural networks are computing systems that mimic the thought process of a human brain and is inspired by biological neural networks. (Chen, Yung-Yao et al., 2019) The data is both unlabelled and unprocessed and leads to learning without human supervision. In deep learning this data can be supervised, unsupervised or semi-supervised. (Jiang, et al., 2017) This method can be used in medical diagnosis applications; to detect heart diseases or acute nephritises disease among other functions. (Al-Shayea, 2011)

6.4 Ethical AI and Challenges

The field of artificial intelligence in healthcare is relatively new, the subject of digital ethics is even newer. However, in the last decade it has received more

and more attention with the advancement of healthcare informatics. As with every new technological development there is the voices of those who challenge it. (Müller, 2020) Those concerned with the advances of AI in the field of healthcare question the risks related to patient privacy and electronic health records (EHR). (Cohen, et al. 2014)

The use of AI applications in the field of healthcare that meet the criteria of ethical standards is something that must be discussed. It is crucial that the healthcare system is ethically and legally supervised when AI is being applied in the field. According to the latest research, consent and privacy are the main concerns when contemplating the ethical and legal challenges of artificial intelligence application in healthcare. (Gerke et al., 2020)

7 Scoping Study

The following text utilizes Table 2 from sub-chapter Scoping Research Method. The Levac et al, 2010 framework is used to conduct a rapid scoping review for the research questions: “How does artificial intelligence impact medical device regulations in the EU and the United States?” and “How does the EU medical device regulations compare to the US FDA legislation in respect to artificial intelligence in medical devices?”.

7.1 Identifying the research question

Formulating a well-constructed research question is essential for a successful scoping review. The PICO (Population-Problem-Patient, Intervention, Comparison and Outcomes) method is a mnemonic used to capture the key elements of a good clinical foreground question. (Aslam & Emmanuel, 2010). Not all scoping review research questions can be defined using the PICO process (or framework) because most scoping reviews are uncharted territories with more complex and exploratory research questions. (Munn et al., 2018) The process of identifying the research question for a scoping review can be quite complex and take multiple tries before getting it right. (Aromataris and Munn,

2020) identifying of the research question and its keywords was done by implementing the commonly used systematic review tool PICO. Table 5 showcases a breakdown on the question statement and application of the method. The initial keywords selected for database search engines were built upon the PICO research question of, “How does artificial intelligence impact medical device regulations in the EU and the United Sates?”.

Table 5. Research Question Statement: How does artificial intelligence impact medical device regulations in the EU and the United States?

Question Type	**P**roblem	**I**ntervention	**C**omparison	**O**utcome
Medical Technology	How does artificial intelligence	medical device regulations	in the EU and the US?	impact

Table 7 one can see the primary keywords needed for the topic and initiate the first search on all three electronic search databases. The specific primary keywords used are: Artificial Intelligence, Medical device, Medical Device Regulation, USA, and EU.

7.2 Systematic search

Systematic search is usually conducted in a full systematic review when extracting subject related data by using the correct keywords. In this case the following systematic search is implemented in a scoping review and as such will be more flexible in nature as a research tool.

7.2.1 Data collection

The selected studies are collected from internationally known and recognized databases; (1) ScienceDirect, which is a large domain containing scientific

journals from different scientific branches, (2) PubMed, a similar domain which contains a sufficient quantity of medical- and technological scientific literature and (3) ProQuest Central, the search engine provides access to scholarly journals and other materials such as e-books and multimedia content including videos and audio files. The search engine is connected to various other multidisciplinary databases which lead to a high number of hits with each query unless restrictions (keywords, query modifiers such as nesting terms etc.) are used for better results.

The selected search engine was curtailed by using only recently published studies (years 2017 - 2021), because the focus of this paper only takes into consideration the updated version of EU Medical Device Regulation which came into action in early 2017 and will be fully finalized by 2021. All scientific studies and review articles, which were at the search time, accessible by the Metropolia UAS credentials belonged to the selection pool. If the articles generated from the systematic search does not contribute to finding a solution to the research question, then it is not considered for this study. Table 6 shows the criteria for this systematic search.

Table 6. Inclusion and exclusion of the systematic search

Contents of the systematic search	**Not included in the systematic search**
Content material must be written in English	Articles in any other language except English
Journal articles, research articles and review articles published between the years 2017 and 2021	Journal articles, research and review articles published before the year 2017
Text accessible through Metropolia UAS credentials. Full-text and peer-reviewed	Articles behind paywalls and institutional rights not accessible by Metropolia UAS. Only partial text or abstract. Not peer reviewed.
Studies and review articles that focus on medical device legislation focusing on the United States or the EU Member states	Articles and studies that are not related to medical device legislation in the United States or the EU Member states

Included studies and articles must be related to the application of artificial intelligence in medical devices or medical diagnosing	Article which focuses on only one of the research topics: medical device legislation and policymaking or artificial intelligence and its various applications

The systematic search was conducted between mid-August and late September 2021, and the results shown below are reflective of that time period. Of the three chosen electronic search engines each initial search result was generated without any constrains and yielded a vast number of publications. The results produced by these databases gave us scientific studies, articles, books with subject related chapters and much more. When one of the selected search engines, ScienceDirect hit 4,773 results from the search query “Artificial Intelligence” AND “Medical Device Regulation”, the chose was to exclude all other material that were not full-text and peer-reviewed. Which meant that other literature forms such as editorials, encyclopaedias, book chapters, discussion papers etc. were excluded from the database search.

The second search, with only research articles and review articles chosen, produced 1,682 hits. This result output came after initiating the following constrains i.e., filters to the search query; publication years (2017-2022), language (English) and full-text accessibility via Metropolia UAS credentials. In the end, the second initial search resulted in fewer number of publications but still in the thousands. Skimming through the article headlines based upon relevancy, made it possible to see that the selected material was related in some respects to the primary keywords “Artificial Intelligence” and “Medical Device Regulation”, but rarely in relations to the EU MDR and/or the US FDA medical device legislative process. Our second search retrieval of primary keywords “Artificial Intelligence AND US” gave a staggering 21,150 results, with the above filters included. This meant another look at the PICO-method and research question.

The scoping review search method is iterative which means that one of the main differences between a conservative systematic literature review and a more flexible scoping study is the chance to take in-depth look of the concept

material at hand and then if needed to go back to the drawing board and make further changes that lead to a suitable systematic search strategy. While systematic literature reviews apply inclusion/exclusion criteria early, the scoping literature is more forgiving. In this case, by applying Stage 3 Study Selection of the six-stage methodology framework (Levac et al., 2010) it is possible to map the relevant studies available after viewing the data from selected search engines. This meant in practice branching out to subject related terms to produce a second set of more relevant keywords. A *Post hoc* analysis meant that the research question could be further broadened by modifying it as the following, “How does Artificial Intelligence impact the United States Food and Drugs Administrations medical device legislation and the EU Medical Device Regulation?”. The resulting modification of the PICO mnemonic is showcased in Table 7.

Table 7. Modified Research Question Statement: How does artificial intelligence impact the United States Food and Drugs Administrations medical device legislation and the EU Medical Device Regulation?

Question Type	**P**roblem	**I**ntervention	**C**omparison	**O**utcome
Medical Technology	How does artificial intelligence	**medical device legislation**	**US FDA and EU MDR?**	impact

The modification of the research question gave us access to use the following terms, “medical device legislation”, “FDA” and “EU Medical Device Regulation”, when compiling Boolean strings in search engines for more subject specific information from the selected databases. Through multiple variations of search engine Boolean strings over the course of one and a half month, the keyword “Artificial Intelligence” with the keywords “FDA”, “medical device” and “EU Medical Device Regulation” proved to result in the most relevant research articles and research reviews.

Each search engine database has its own unique approach to the application of Boolean queries, parentheses to wrap the OR search, asterisk for possible variations of the inputted keyword and quotations. This includes ScienceDirect, PubMed and ProQuest which each have a different approach to Boolean query modifiers. For search engines ScienceDirect and ProQuest electronic databases the quotation marks were used to restrict result volume of irrelevant material. Which meant that each search would only show materials related to the subject matter, for example in the case of “artificial intelligence” it would result in the material related to this subject, and not simply intelligence or artificial. Unlike the other two electronic databases, PubMed did not need quotation marks to restrict the volume material as its query without any modifiers yielded minimal results. By the final search retrieval (i.e., filters being applied), more relevant literature was obtained for this scoping study and its results from Appendix 1 are summarized in Table 8.

Table 8. Data screen summary of systematic search retrieval from 22nd of September 2021

Keywords	Database	No. of results from database (unfiltered)	No. of results when hits are filtered	No. of articles chosen for analysis
“Artificial Intelligence” AND “EU medical device regulation”	ScienceDirect PubMed ProQuest	11 5 94	8 1 7	2 0 4
“Artificial Intelligence” AND “FDA medical device”	ScienceDirect PubMed ProQuest	14 81 62	4 6 6	3 3 3
Total		267	32	15

Data charting is formed by building a format to answer the research question. The data is categorized according to the basic information of the article (author(s), title, year of publication and journal issue no.). This information is

collected and categorized, including the possible research method of the research article or review article. Charting this information involves extracting the findings of these texts as well as the conclusions. The summary of all selected studies can be found in Appendix 4.

7.2.2 Results

The chosen texts are eligible based on the inclusion/exclusion criteria set post hoc analysis. The fifteen research articles and review articles were chosen based on title and abstract when skimming through filtered search engine hits. The study selection process was constructed based on Johanna Briggs Institutes critical appraisal tool “Checklist for Text and Opinion” to assess the chosen published text materials trustworthiness, relevance, and results. By slightly modifying questions in the JBI critical appraisal form it was possible to utilize it as a standard assessment template for all 15 of the chosen text materials. The form and example of usage is seen in Appendix 2. The decision to use a pre-existing template was due to the limitations of conducting a scoping study within its pre-set timeframe (Metropolia UAS B.Eng. Thesis 15 ECT the equivalent of 400 hours of productive worktime). An example of a filled critical appraisal form is in Appendix 3.

It is to be noted that some of the filtered results showed records titled as full issues of an entire volume from scholarly journals instead of subject related articles. The full issues are taken into consideration when charting the data and are showcased in Table 10. The issues were removed from the selection pool manually through MS Office Excel spreadsheet to further validate the article selection pool. With the expertise of Metropolia library information specialist, the recorded searches were documented and analysed to reflect the best possible outcome. The figure below illustrates the article selection progress by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) - method for scoping reviews. It depicts the flow of information at every stage of the systematic search; records identified, included/excluded, and reasons for exclusions. Figure 8 horizontally indicates the number of articles left after each

appraisal stage. The stages are illustrated vertically: Identification, Screening, Eligibility and Included. The final result yielded 15 articles that were chosen for the scoping study result.

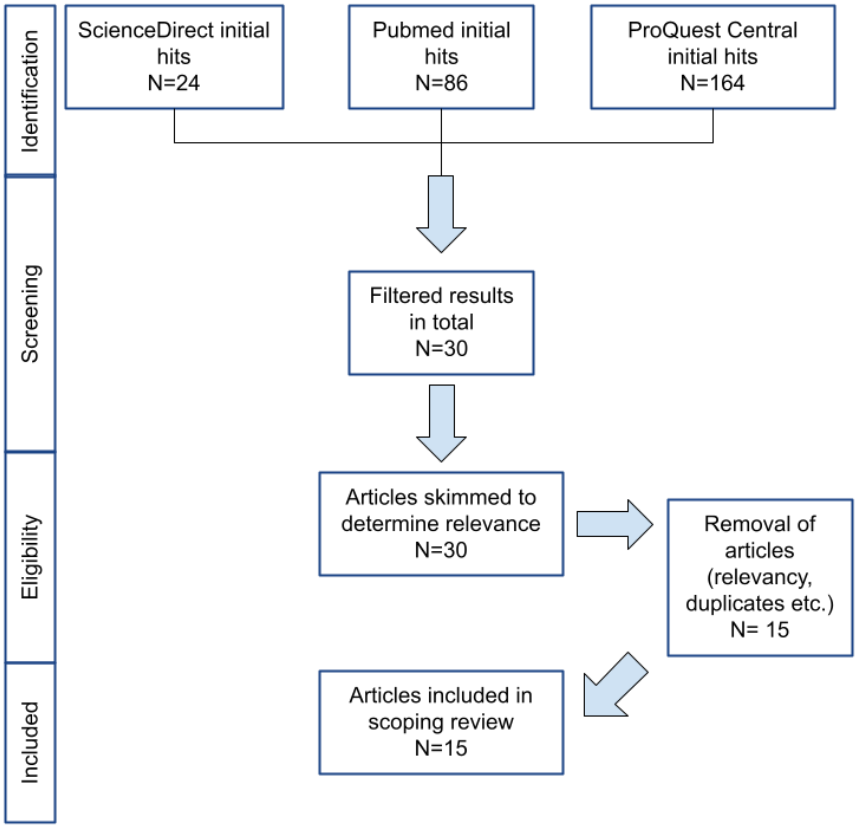

Figure 8. PRISMA-diagram of the article selection process

The PRISMA-diagram is an ideal flowchart when illustrating the required process to the filter out unnecessary articles and other documents that show up in the search results. The 30 articles from ScienceDirect, ProQuest Central and PubMed included duplicated, irrelevant documents, full issues of journal volumes, which were ultimately discarded from the final selection as showcased in the flow chart.

7.3 Discussion of results

The results were quite limited with only 6 articles primarily relevant to the research question. Even then, the research question could only partially be answered due to the focus on regulatory authority being on FDA or EU. The authors discussed in their review/journal article the impacts and effects of AI in the medical/health technology field. (Tschider, 2021; Gerke et al., 2020; Muehlmatter et al., 2021; Pesapane et al., 2018; Beckers et al., 2021; Yaeger et al., 2019)

Overview of results from selected studies

This qualitative synthesis report on the findings of the selected articles can be summarized as primarily related on the current and future applications of AI/ML-based medical devices in the field of medicine and healthcare with little consideration to the cross-national regulations between the United States and EU member nations. It can be contextualized that the research reviews, research studies, white papers etc. from the fifteen chosen text materials strongly indicate that a uniform oversight on artificial intelligence and machine learning regulatory allocations is necessary and must be updated with the same pace of modern medical device innovations. Experts from the field of law and medicine tell of how the conception of AI medical device regulations must be constructed to become more comprehensive and complementary to ensure public safety. (Tschider, 2020) The need for this can be proven due to the existence of the EVIDENCE-checklist.

To fill in the gaps of medical device regulatory authorities the Digital Medicine Society has published the EVIDENCE-checklist which ensures that proper reporting of studies in the field are to be executed. (Manta et al., 2021) This is to reduce cases such as the AI-enhanced mammography screening tool which produced false positive diagnosis, and the FDA in 2018 cleared it based on limited patient control data. (Lee et al, 2019) (ESR, 2019) With multidisciplinary academics coming together and compiling their knowledge and expertise, it is

possible to see into the “black box” and build the necessary tools to clear AI medical device technology to consumers and healthcare professionals.

AI/ML-based MD impact on medical device regulations in the EU and the United States

The FDA has, as some would say, acted accordingly to develop policies and guidelines to the SaMD. It has taken the role as a global leader in medical device regulations by piloting a Software Precertification (Pre-Cert) Program with companies such as Apple, Fitbit, and Samsung. Subsequently, in the EU member states (Brexit not taken into consideration because of the current declaration from the UK authorities complying and conducting the same regulatory approval pathway as the EU member states), a working group led by NHS England has developed “Evidence Standards Framework for Digital Health Technologies”. (Coravos et al, 2019).

Comparison of EU MDR to the US FDA legislation in respect to AI/ML-based MD

Radiology is the leading medical speciality when in concern to AI/ML-based medical devices. FDA has approved of three AI/ML-based medical devices via premarket approval pathways. Two of them were of the radiology speciality, breast cancer detection assistance and breast abnormality detection assistance. In the EU, vastly similar AI/ML-based medical devices (radiology devices that support cardiac MRI and CT post-processing workflows) where given the risk class III and given market approval.

It is difficult to outline the differences between the two regulatory authorities due to the lack of evidence when analysing the EU safety and performance approach to the regulation of MD. (Pesapane et al., 2021) This is because of the decentralized approach to the CE-mark, the confidentiality of Notified Bodies and the lack of publicly available registry of approved medical devices. (Muehlmatter et al., 2021)

7.4 Reliability

The author has documented the search engine results, filters and keywords that were produced during this intensive search period and kept the documents saved on a password protected USB drive for future references for proof of research quality and reproducible search strategy. The Johanna Briggs Institutes Critical Appraisal Form for Systematic Appraisal of text and opinion was applied for validating the research conducted in this scoping study. This gives credibility to the appraised articles and its scientific results/conclusions/findings.

8 Conclusion

This thesis presents the findings of the scoping study which tried to answer the impact of AI/ML-based medical devices on the European Union Medical Device Regulation and the United States Foods and Drugs Administrations medical device regulatory approval pathways. The limited number of suitable research studies and other types of scientific documents narrowed the research findings but gave a definitive answer on how to approach the new world of AI technology regulations and privacy issues that the General Data Protection Agency (GDPR) of today cannot yet foresee. A complete overhaul of the system may yet be in the future but for now there is no conclusive decision to be made.

The road to discovery has always been tricky but with the dreams of modern fiction, artificial intelligence is developing fast. There is no doubt, AI has the potential to transform various areas on healthcare and help the increasing economic burden on the healthcare system which faces a daunting task in the next 25 years. It can be concluded that much more (scoping) studies will be conducted on this subject in the near future.

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Appendix 1 Systematic search conducted on between 29th and 30th of Sept 2021

Systematic electronic database (ScienceDirect, PubMed, ProQuest Central) search for scoping review based on post hoc analysis.

PICO Research Question: How does Artificial Intelligence impact the United States Food and Drugs Administration medical device legislation and the EU Medical Device Regulation?

PICO derived keywords: “Artificial intelligence”, “medical device regulation”, “medical device”, “FDA”, “EU Medical Device Regulation”

Search string: “keyword” AND “keyword keyword” for example “Artificial intelligence” AND “FDA medical device”

Filters for all databases: Years (2017-2021), Language English, Full-text, Peer-reviewed

Table 9. Electronic database specific filters

Database	Filter type	Filter
ScienceDirect	Document type	Research article, Review article
ProQuest Central	Document type	Article
PubMed	Document type	Classical article, Review article

Full data screen results and search keywords usage output from systematic search conducted on 29th and 30th of September 2021 for thesis scoping review on the impact of artificial intelligence on medical device regulations and legislation in the EU member states (including the United Kingdom post Brexit) and United States of America. Results are showcased in the next page of the appendix.

Table 10. Data screen results and article selection

Database	Keywords	Results without filter	Results with filter	Chosen based on R.Q. relevancy
ScienceDirect	Artificial intelligence, FDA medical device	14	4	3
	Artificial Intelligence, EU Medical Device Regulation	11	8	2
PubMed	Artificial intelligence, FDA medical device	81	6	4
	Artificial intelligence, EU Medical Device Regulation	5	1	0
ProQuest Central	Artificial intelligence, FDA medical device	62	6	4
	Artificial intelligence, EU Medical Device Regulation	94	7	2
Total		267	32	15

Appendix 2 JBI Critical Appraisal Checklist for text and opinion papers

Reviewer_____
Date_____

Author_____Year_____

	Yes	No	Unclear	Not applicable
1. Is the source of the opinion clearly identified?	☐	☐	☐	☐
2. Does the source of opinion have standing in the field of expertise?	☐	☐	☐	☐
3. Are the interests of the relevant population the central focus of the opinion?	☐	☐	☐	☐
4. Is the stated position the result of an analytical process, and is there logic in the opinion expressed?	☐	☐	☐	☐
5. Is there reference to the extant literature?	☐	☐	☐	☐
6. Is any incongruence with the literature/sources logically defended?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐
Comments (Including reason for exclusion)

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Appendix 3 JBI Critical Appraisal Example

Reviewer: Bushra Nawar

Date 1.10.2021

Author: Pesapane et al. Year 2018

	Yes	No	Unclear	Not applicable
1. Is the source of the opinion clearly identified?	X	☐	☐	☐
2. Does the source of opinion have standing in the field of expertise?	X	☐	☐	☐
3. Are the interests of the relevant population the central focus of the opinion?	X	☐	☐	☐
4. Is the stated position the result of an analytical process, and is there logic in the opinion expressed?	X	☐	☐	☐
5. Is there reference to the extant literature?	X	☐	☐	☐
6. Is any incongruence with the literature/sources logically defended?	X	☐	☐	☐

Overall appraisal: Good Include X Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

Article has regulatory differences and privacy issues between EU MDR and US FDA authorities.

Appendix 4 Description of selected articles

Author Year Country	Title	Source	Document type	Aims/purposes	Findings and conclusions	Key findings related to the review question
Beckers, R., Kwade, Z. and Zanca, F. 2021 Belgium	The EU medical device regulation: Implications for artificial intelligence-based medical device software in medical physics	Physica Medica, Volume 83, Pages 1-8	Research article	To give medical physicist experts (MPE) perspective on how the EU MDR affects the development of AI based medical device software.	MPE should have key involvement concerning AI based software in the medical technology field. AI means more training and upskilling of healthcare professionals	EU MDR affects AI development and its regulatory pathways.
E. Fosch-Villaronga, T. Mahler 2021 Netherlands and Norway	Cybersecurity, safety and robots: Strengthening the link between cybersecurity and safety in the context of care robots	Computer Law & Security Review, Volume 41,	Research article	“to illustrate cybersecurity challenges and their subsequent safety implications with the concrete example of care robots.”	“policymakers need to consider cybersecurity as an indissociable aspect of safety to ensure robots are truly safe to use.”	The application of artificial intelligence in healthcare robotics and its cybersecurity risks related to EU MDSW

K. Yaeger, M. Martini, G. Yaniv, E. Oermann, A. Costa 2019 United States	United States regulatory approval of medical devices and software applications enhanced by artificial intelligence	Health Policy and Technology, Volume 8, Issue 2, Pages 192-197	Research article	“to discuss the evolution of US FDA oversight of medical devices, initially of hardware, and the present stance on medical software applications, including devices augmented with artificial intelligence.”	“FDA has reacted accordingly by clearly defining the various medical software applications and set goals to improve the regulatory approval process of lower risk medical software platforms and devices.”	US FDA and its relations to AI development. FDA guidance on artificial intelligence (AI) applications
C. Lee, N. Houssami, J. Elmore, D. Buist 2020 United States	Pathways to breast cancer screening artificial intelligence algorithm validation	The Breast, Volume 52, Pages 146-149	Research article	“to outline lessons learned from prior efforts in the field”	“the need for a framework for continuous monitoring and recalibration of these AI tools.”	Brings attention to the need of external validation with AI screening mammography. FDA tackling issues with stakeholder invested AI MD by improving

						regulatory processing
S. Parasa, M. Wallace, U. Bagci, M. Antonino, T. Berzin, M. Byrne, H. Celik, et al. 2020 United States	Proceedings from the First Global Artificial Intelligence in Gastroenterology and Endoscopy Summit	Gastrointestinal Endoscopy, Volume 92, Issue 4, Pages 938-945.e1,	Research article based on the Summit	"to report the findings of a group of experts focusing on issues in AI research and applications related to gastroenterology and endoscopy."	Gastroenterology is a prime candidate for early adoption of AI.	"no FDA-cleared or -approved devices that use AI endoscopy image-based detection or characterization for colon polyps because the practical usefulness is unclear."
C. Tschider 2021 United States	Medical Device Artificial Intelligence: The New Tort Frontier	Brigham Young University Law Review, vol. 46, no. 6, pp. 1551-1616	Journal article	To identify key preemption issues for AI machines in the FDA regulatory pathways	Explains that a more comprehensive and complementary safety and compensatory model should be implemented when dealing with AI machines. Recommends alternative regulatory	"(FDA), the administrative agency responsible for overseeing the safety and efficacy of medical devices, has not effectively addressed AI system

					allocation for AI machines.	safety issues for its clearance processes.”
Coravos A, Goldsack JC, Karlin DR, Nebeker C, Perakslis E, Zimmerman N, et al. 2018 United States	Digital Medicine: A Primer on Measurement	Digital Biomarkers, vol. 3, no. 2, pp. 31-71.	Review article	To introduction core concepts and terms that define digital medicine by “outlining the security, ethical, regulatory, and legal issues” which must be considered.	“Clarifying language and establishing a standard lexicon will advance the field faster, together, and with more trust.”	Digital medicine in concern to AI algorithms and its regulatory aspect in regard to the FDA medical device clearance and approval
O'Keeffe, M., Barratt, A., Maher, C., Zadro, J., Fabbri, A., Jones, M. & Moynihan, R. 2019 United Kingdom	Media Coverage of the Benefits and Harms of Testing the Healthy: a protocol for a descriptive study	BMJ Open, vol. 9, no. 8.	Journal Article	To “examine the media coverage of the benefits and harms of testing the healthy, and coverage of potential conflicts of interest of those promoting the testing.”	To conduct a study based on 5 tests that determine the overly positive media attention given to new medical innovations	Concerns of lack of robust clinical research and potential to lead to false positives and overdiagnosis. The FDA does not take this into consideration.
Manta, C., Mahadevan, N.,	EVIDENCE Publication	Digital Biomarkers,	Journal article	“to promote high quality reporting	“EVIDENCE checklist will	The Digital Medicine Society

Bakker, J., Simal Ozen Irmak, Izmailova, E., Park, S., Poon, J., Shevade, S., Valentine, S., Vandendriessche, B., Webster, C. & Goldsack, J.C. 2021 Switzerland	Checklist for Studies Evaluating Connected Sensor Technologies: Explanation and Elaboration	vol. 5, no. 2, pp. 127-147.		in studies where the primary objective is an evaluation of a digital measurement product or its constituent parts"	serve as a much-needed guide to raise the bar for quality reporting in published literature evaluating digital measurements products."	has come up with a checklist for evaluating digital measurement products or its constituent parts. This was done to promote high quality reporting in the field of medical technology in US
Springer Nature B.V. 2019 Netherlands	What the radiologist should know about artificial intelligence – an ESR white paper	Insights into Imaging, vol. 10, no. 1, pp. 1-8.	Journal Article	"to provide a review of the basis for application of AI in radiology, to discuss the immediate ethical and professional impact in radiology, and to consider possible future evolution."	"AI coupled with CDS can improve the decision process and thereby optimise clinical and radiological workflow"	AI medical devices "should be subject to same form and standard of regulation as any other medical device or product, as provided for by the FDA (in the US) or the EU Medical Device Regulation"
Majumder, S. & Deen, M.J	Smartphone Sensors for Health	Sensors, vol. 19, no. 9.	Journal Article	To "present a comprehensive	"future research perspectives and	"A discussion on regulatory

2019 Switzerland	Monitoring and Diagnosis			review of the state-of-the-art research and developments in smartphone-sensor based healthcare technologies.”	concerns regarding smartphone-based healthcare systems are described.”	policies for medical devices and their implications in smartphone-based healthcare systems is presented.”
Pesapane F, Volonté C, Codari M, Sardanelli F. 2018 Italy	Artificial intelligence as a medical device in radiology: ethical and regulatory issues in Europe and the United States	Insights into imaging, 9(5), 745–753	Review article	To “analyse the legal framework regulating medical devices and data protection in Europe and in the United States, assessing developments that are currently taking place.”	“Regulations for safety, privacy protection, and ethical use of sensitive information are needed.”	Regulatory differences and privacy issues between EU MDR and US FDA authorities. “EU laws consider cyberattacks, incidents (notification and minimisation), and service continuity. U.S. laws ask for opt-in data processing and use as well as for clear consumer consent. “

Muehlematter, U. J., Daniore, P., & Vokinger, K. N. 2021 Switzerland	Approval of artificial intelligence and machine learning-based medical devices in the USA and Europe (2015-20): a comparative analysis	The Lancet. Digital health, 3(3), e195–e203	Review article	“to identify and analyse AI/ML-based medical devices approved in the USA and CE marked in Europe between 2015 and 2020.”	The importance to discuss on how to regulate AI-based medical devices whether more rigorous regulations for approval are needed. Need of more transparency to enable and improve efficacy, safety, and quality of AI-based MD	Overview of medical device regulation in the USA and Europe. And comparison between US and European policy implications when dealing with AI-based MD.
Gerke S, Babic B, Evgeniou T, Cohen IG. 2020 United States	The need for a system view to regulate artificial intelligence/machine learning-based software as medical device	NPJ digital medicine vol. 3 53.	Review article	“that regulators like the FDA need to widen their scope from evaluating medical AI/ML-based products to assessing systems.”	“AI/ML-based SaMD pose new safety challenges for regulators. They need to make a difficult choice: either largely ignore systemic and human factor issues with each approval and subsequent update”	FDA regulatory pathway and EU MDR need to update policymaking because AI and ML based software in MD pose challenges for regulators in the current regulations framework.

Jim HSL, Hoogland AI, Brownstein NC, et al. 2020 United States	Innovations in research and clinical care using patient-generated health data	CA: a cancer journal for clinicians, 70(3), 182–199.	Review article	“to provide an overview of the current clinical, regulatory, technological, and analytic landscape as it relates to PGHD in oncology research and care.”	“the potential benefits of PGHD make them increasingly likely to be integrated into oncology research and clinical care”	“Analytic opportunities regarding PGHD are envisioned in the context of big data and artificial intelligence in medicine.”