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Coordinating Research and evidence for Medical Devices (CORE MD) and beyond

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Abstract

Medical device regulations have its focal center on translating expert knowledge into advice for EU regulatory guidance, and building expertise in regulatory science in the clinical community, the Coordinating Research and Evidence for Medical Devices (CORE MD) project is here to review methodologies for the clinical evaluation of high-risk medical devices and recommend new designs to set an appropriate balance between innovation, safety, and clinical effectiveness. CORE-MD is a European Union Horizon 2020 project which began in April 2021 and was concluded in March 2024. For the first time ever CORE–MD consortium stands to bring together 33 medical associations, on one platform. The major objective of CORE MD is, developing guidance for evaluation of artificial intelligence. CORE MD includes cardiovascular, and diabetes medical devices, since these exemplify devices are used to reduce mortality and morbidity, the use of real-world evidence in regulatory decision making, evidences from clinical trials on High-risk medical devices, establishment of post approval evidence development schemes, tools to retrieve public information on medical devices and information on the performance of these High-Risk Medical Devices. As a result, the need for more sources to provide clinical evidences for medical devices is required, before they are approved for implantation in patients and to add on the focus, CORE MD project has brought brilliant potential in increasing the use of benefit measures and accelerating surrogate outcomes research which would optimize an implant's benefit-risk ratio and making CORE-MD an ambitious project with great scope.

Keywords: Medical Device; CORE MD; Clinical Evaluation; Europe Union; Medical Device Regulation (MDR); CE Mark

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1. Introduction

CORE MD, A project which is supported by Grant from the European Union Horizon 2020. The Consortium comprises a unique collaboration with wide geographical distribution across Europe including National regulatory agencies and notified bodies as well as public health institutes, Medical Professional associations, academic institutions and patients main tasks was to review existing evidence to develop new methods for General clinical evidence and to investigate how to extract maximal information from Real World data. The task was to critically assess publicly available clinical investigations used in the evaluation of specific high-risk cardiovascular devices and identify differences in study designs before and after CE Mark approval during a period of 20 years. The use of medical devices in diabetes has increased exponentially over the past three decades. Unfortunately, however, during this time and despite the many products that have become available, legislation covering the safety, effectiveness, and reliability of these devices has remained less than perfect.

The draft legislation to revise the registration and regulation of medical devices in Europe mainly affects class 3 medical devices. The few changes that are proposed will not satisfy many in the medical community who are calling for tougher, more stringent, and uniformly recognised legislation and guidelines when it comes to production and the use of medical devices in diabetes and all other areas of medicine. (1) The European Union (EU) Medical Device Regulation (MDR) 2017/745 challenges the medical community to engage with regulators, notified bodies and industry to develop transparent, rigorous, and proportionate methods to evaluate the clinical efficacy and safety of medical devices and monitor their performance. As a component of the CORE-MD project funded by the EU Horizon 2020, a comprehensive analysis was conducted on the existing scientific literature pertaining to surgical heart valve replacements for native aortic and mitral valve conditions. (2) There will also be a focus on cardiovascular, and diabetic devices which are the major high-risk devices whose real-world evidences and clinical evaluations are conducted using different methodologies. Establishment of post marketing surveillance and clinical evaluation on AI in medical devices and information on

the performance of these High-Risk Medical Devices are determined.

There will also be a focus on cardiovascular, and diabetes devices, since they exemplify devices used to reduce mortality and morbidity, use of real-world evidence in regulatory decision making, evidences from clinical trials on High-risk medical devices, establishment of post approval evidence development schemes, tools to retrieve public information on medical devices and information on the performance of these High-Risk Medical Devices

2. CORE-MD:

- CORE-MD is the first formalised group of stakeholders in Europe working together to identify ways to enable the scientific, fair, and systematic evaluation of high-risk medical devices.
- The CORE-MD project comes at a timely moment, following the Adoption of the new EU Medical Devices and In Vitro Medical Devices Regulations, which has entered into effect on 26 May 2021(Medical Devices), and 26 May 2022 (In Vitro Medical Devices). (3)

The Treaty on the Functioning of the European Union states that the European Commission and Member States can take joint measures "setting high standards of quality and safety for medicinal products and devices for medical use" when it is necessary for a high level of human health protection (Article 168, paragraph 4c).

In 2017 the EU Medical Device Regulation (MDR) (EU 2017/745) increased requirements for clinical investigations of devices before their approval, and reinforced the need for post-market surveillance. The approval led to a notable rise in the Medical Technology Unit's responsibilities within the Directorate General for Health and Food Safety of the European Commission (DG SANTE), which oversees the execution of the MDR but the increase in manpower that was recommended in the Impact Assessment did not occur.

The Horizon 2020 research call [SC1-HCO-18-2020] asked for proposals to create methodological approaches that would enhance the clinical investigation and assessment of high-risk medical devices. The grant was awarded to the CORE-MD consortium and the work was conducted from 1st April 2021 to 30th March 2024. This booklet highlights the key outputs. (4)

2.1 There were 4 main objectives of CORE-MD

- To investigate the methodologies of clinical investigations that have been used to evaluate high-risk cardiovascular, orthopedic, and diabetic medical devices.
- To review and recommend alternative designs of clinical studies that can provide high-quality clinical evidence for new high-risk medical devices.
- To review and develop methods for aggregating clinical data from registries and other real-world sources across the life-cycle of high-risk medical devices.
- To foster exchanges and networking between academic centers and across medical specialties, with notified bodies, regulators, manufacturers, health technology assessment bodies, and patients.(**4**)

2.2 Breakdown of the Initiative

CORE–MD aims to convert specialized scientific and clinical knowledge about research methods for assessing high-risk medical devices into guidance for EU regulators, in order to strike an optimal equilibrium between innovation, safety, and efficacy. This endeavour will involve a distinctive partnership among medical organizations, regulatory bodies, accredited organizations, universities, patient advocacy groups, and health technology assessment agencies. (5)

2.3 The consortium

The consortium includes 22 partners involved in the development, evaluation, approval and certification, clinical use, and monitoring of medical devices.

They are European Society of Cardiology, Insel Gruppe Ag (University Hospital Bern), Katholieke Universiteit Leuven, UMIT - University for Health Sciences, Medical Informatics and Technology, University of Gothenburg, Politecnico di Milano, Health Products Regulatory Authority, Danish Medicines Agency, Office for Registration of Medicinal Products, Medical Devices and Biocidal Products ,National Institute for Public Health and the Environment, Italian National Institute of Health, European Federation of the National Associations of Orthopaedics and Traumatology, HTA Austria - Austrian Institute for Health Technology Assessment GmbH, Progress and Health Foundation, European Association for Medical Devices of Notified Bodies, Biomedical Alliance in Europe, European Academy of Paediatrics, European Patients Forum, Leiden University Medical Centre (LUMC), The Chancellor, Masters and Scholars of the University of Oxford, Region Uppsala Royal College of Surgeons in Ireland. (6)

The European Society of Cardiology is leading the consortium, working closely with the European Federation of National Associations of Orthopaedics and Traumatology, and it includes all 35 specialist medical associations that are part of the Biomedical Alliance in Europe. The ultimate recommendations will be presented to the European Commission's Working Group on Clinical Investigation and Evaluation to be taken into account during the development of EU guidance or common specifications, which is represented in Figure 1**.** (7)

2.4 Work Packages

There are five work packages that make up the CORE-MD project and the flow of these work packages is shown in Figure 2.

- Understanding the techniques used to produce clinical evidence for high-risk medical devices is the goal of Work Package 1.

- Work Package 2 investigates novel approaches to performance data generation with the goal of enhancing the clinical evidence for high-risk medical devices.
- Work Package 3's primary goal is to get the most out of real-world evidence and medical device registries.
- Work Packages 4 and 5 will concentrate on project management and stakeholder engagement, respectively. (4)

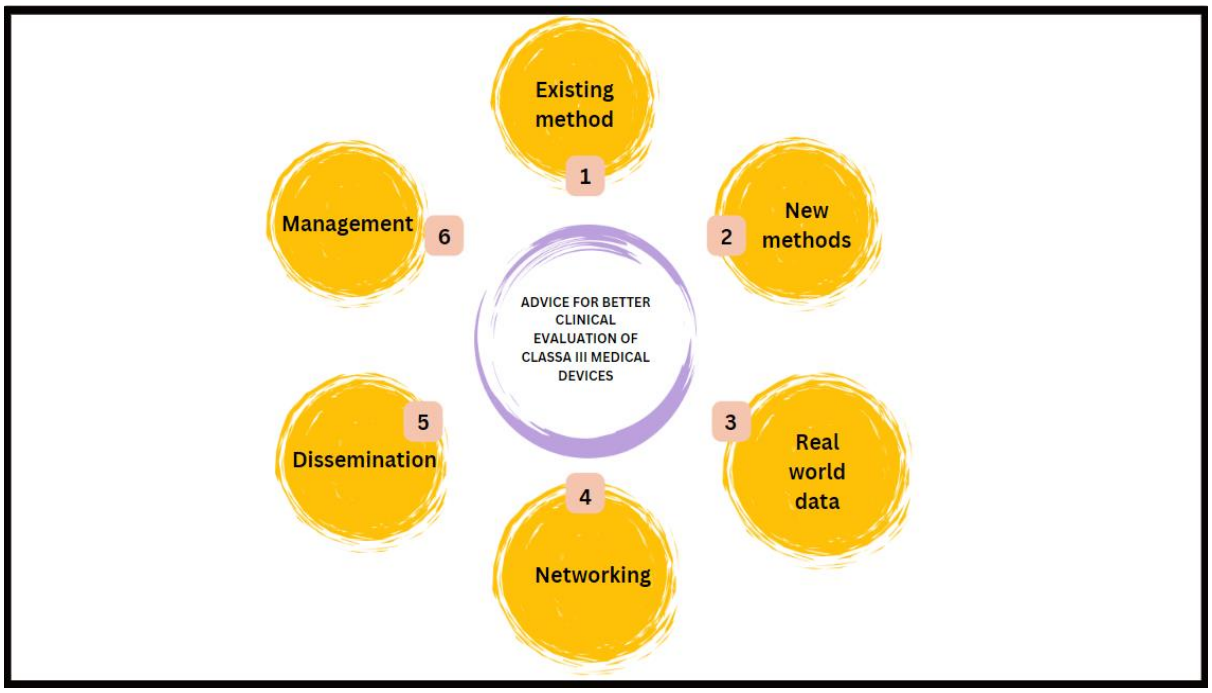


Figure 1. Advice for better clinical evaluation of Class III medical device

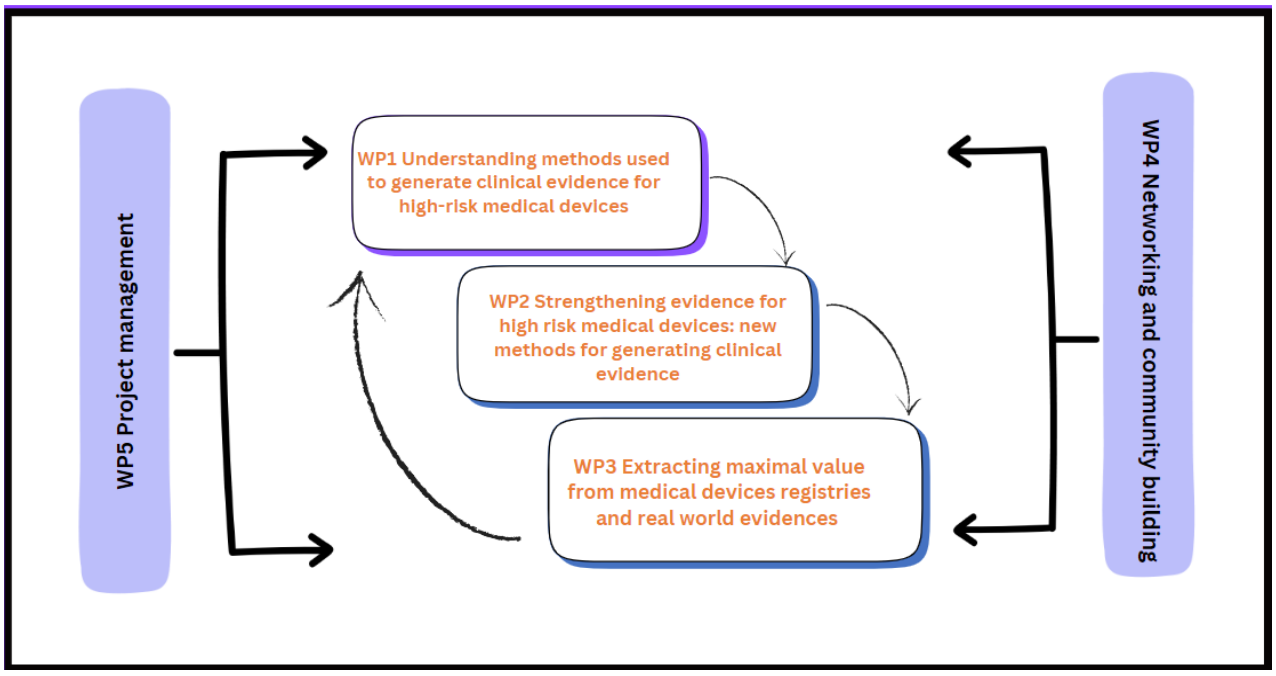


Figure 2. The work packages workflow

3. Risk Based Classification of Medical Devices in EU

The classification in use by the EU medical device regulation is a risk-based system taking into account the vulnerability if the human body and the potential risks associated with the device. In order to confirm the safety and performance, including clinical benefits, of a device, clinical evaluation is "a systematic and planned process to continuously generate, collect, analyze, and assess the clinical data pertaining to a device" (MDR Article 2.44). (8) In European Union the medical devices are classified into three classes as shown in Figure 3.

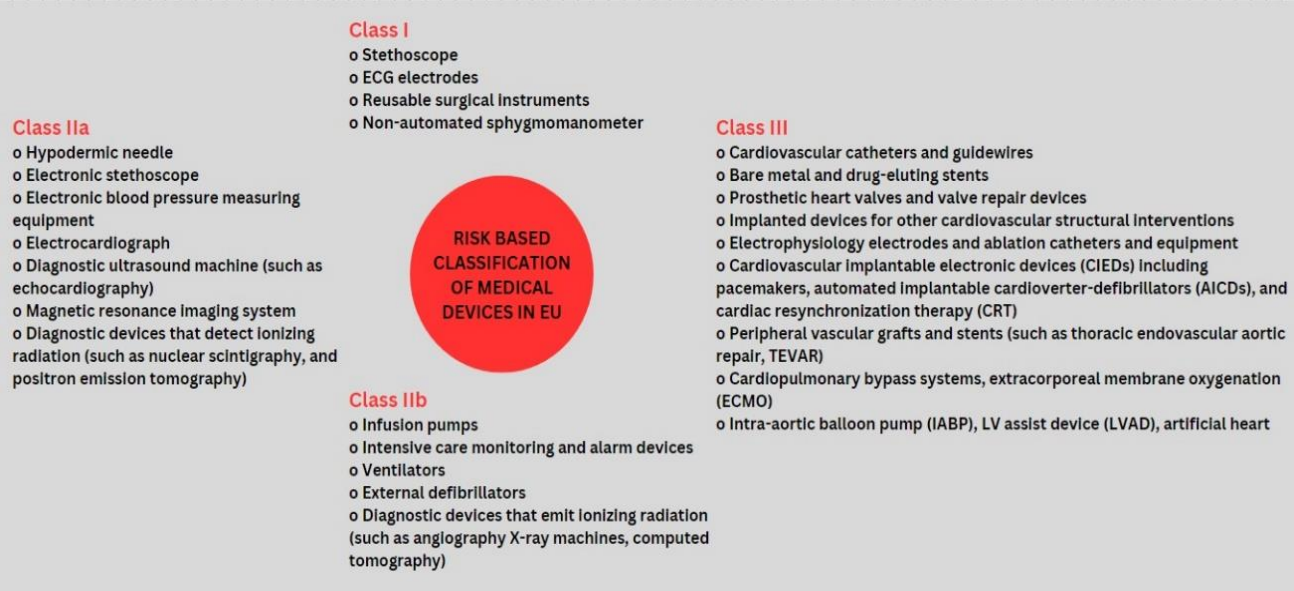


Figure 3. Risk based classification of medical devices in EU

4. Clinical Evaluation of Medical Devices

Clinical examination is necessary in the MDR, irrespective of the device's risk categorization. Verifying conformity with the general safety and performance requirements is the aim of this examination (Article 61). The device must meet a number of criteria, including safety, acceptability of the benefit-risk ratio in relation to the state-of-the-art, and the capacity to perform as intended (Annex I). When comparing the MDR to the MDD, the MDR increases the bar for requirements to be satisfied in clinical review and gives greater weight to clinical data gathered once the device is commercially available. Compared to the MDD, the Regulation specifies more specific requirements for clinical examination. Partially, it accomplishes this by adding sections of a 2016 MDDEV 2.7/1 (rev. 4) non-binding guideline on clinical evaluation. The steps of clinical evaluation for medical devices outlined in the MDR and described in more detail in the MEDDEV 2.7 include creation (and updating) of a clinical evaluation plan; identification of pertinent clinical data (both produced by the manufacturer and available in scientific literature) and of gaps in the available evidence through a systematic literature review, examination of the data that are already accessible, taking into account their methodological soundness, scientific validity, and applicability to the device's clinical assessment; clinical Research (using human subjects), which is required for class III and implantable devices but only required for other devices in order to fill in evidence gaps; examination of all pertinent clinical data to determine if (Annex XIV of the MDR). Manufacturers are permitted to use clinical data from a CE-marked device for clinical evaluation and to assert that their device under evaluation is equivalent to one that already has a CE mark thanks to the MDD and MDR. However, the MDR's (Annex XIV) criteria are more stringent than the MDD's, therefore it's unlikely that producers of medical AI devices will choose to employ this alternative. (9) To be legally marketed in Europe, all medical equipment, including MML devices, and in vitro diagnostic medical devices, must generally meet the CE marking standards under the applicable EU regulatory frameworks. (10) In order to confirm the safety and performance, including clinical benefits, of a device, clinical evaluation is "a systematic and planned process to continuously generate, collect, analyze, and assess the clinical data pertaining to a device" (MDR Article 2.44). (8)

The new EU Regulation (EU) 2017/745 on medical devices, which took effect on May 26, 2017, is crucially important for medical device manufacturers and CE certification, as well as the recertification of their products. Regarding clinical evaluation, this contribution highlights the key distinctions between EU Regulation 2017/745 and EU Directive 93/42/EEC in the following six domains:

(i) Heightened standards for clinical evidence and safety of clinical efficacy,

(ii) Categorization,

(iii) Clinical evaluation, possibly including clinical trials,

(iv) Post-market clinical surveillance,

(v) Clinical reporting and documentation, and

(vi) Establishing the scrutiny procedure of the European Commission. (11)

5. Application of CORE -MD project in EU

5.1 Case Study 1: High Risk Cardiovascular Medical Devices EU Overview/Evaluation

Over the past 20 years, cardiovascular devices have been made available for clinical use in the European Union. Less than 45% of the 5,000 clinical trials that Science looked at from 2010 to 2020 had their data submitted to clinicaltrials.gov on time or early. The identified violations include trials in almost every area of medicine. (12) Up to seven years after completion, 49% of studies on 177 new cardiovascular devices had been published. (13) Of these, 92 mandated and completed post-approval investigations had no published clinical results for 49% of the devices. In another trial evaluation among more than 13,000 trials registered in clinicaltrials.gov was completed between 2008 and 2012 randomly 13% reported summary results at

12 months specifically for cardiovascular devices and a cross-section analysis showed that many clinical trials for high-risk cardiovascular devices approved by FDA remained unpublished and finally it has been also shown that more than 40% of post approval studies had not been published in 5 years. (14)

The need for transparency of clinical evidence for medical devices in Europe

Information should be in the public domain for any approved high risk medical devices and the information required is described in Figure 4

In Europe the key objective of regulatory reforms is to promote higher levels of evidence before high-risk medical devices are approved. Previously many devices were authorized without being supported by clinical trials however nowadays basic information and clinical evidence is expected to be in the public domain for any approved high-risk medical device. (15)

Background: European cardiovascular medical device environment

Figure 4. The Information required to be in the public domain for any approved high risk medical devices

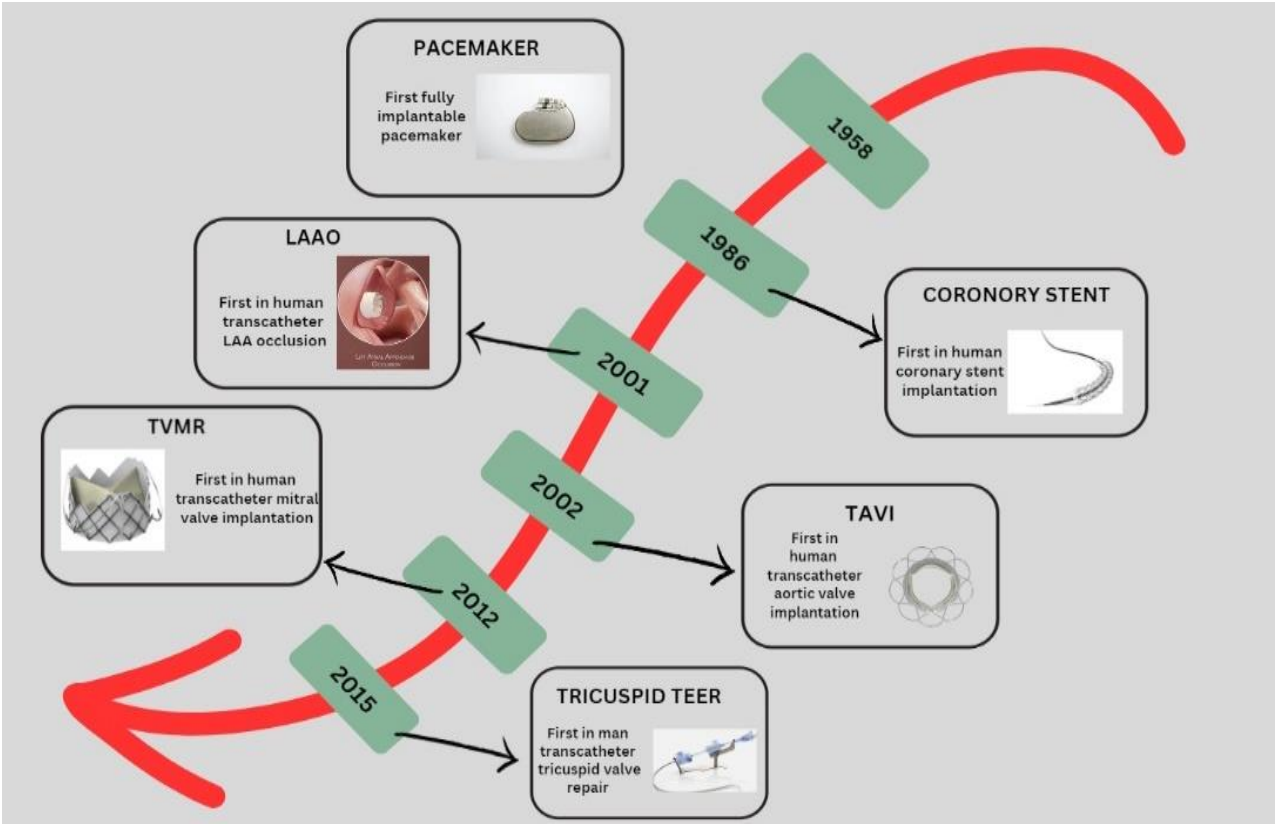


Figure 5. European cardiovascular medical device environment

European investigators have played a key role in the development of high-risk cardiovascular devices with first in human studies performed in Europe followed by device requirements and iterative studies, Using the first pacemaker and coronary artery transcatheter are two examples as shown in Figure 5. Currently, the cost of

repairing aortic valve and mitral valve implantation devices exceeds 5,00,000 for medical devices. The European Union Market and medical technologies are governed by laws that address the performance and safety of devices over the course of their entire lives. In Europe, medical devices are classified using a risk-based system that takes into consideration both the potential risks associated with a given device and the vulnerability of the human body. (16)

Study design recommendations in guidance documents:

- Legally binding for market approval in the EU
- ISO 14155: 2020 clinical investigation of medical devices for human subjects

PRE-MARKET: First inhuman feasibility clinical investigation (Pivotal clinical investigation)

POST MARKET: Post market clinical investigation (Registry)

Further guidance documents:

- RCT for pivotal clinical investigation for heart valves and resorbable devices (ISO 5489, ISO 17137)
- multi centre trials for stents graphs patches (ISO 7198, ISO 12417, ISO 25539)

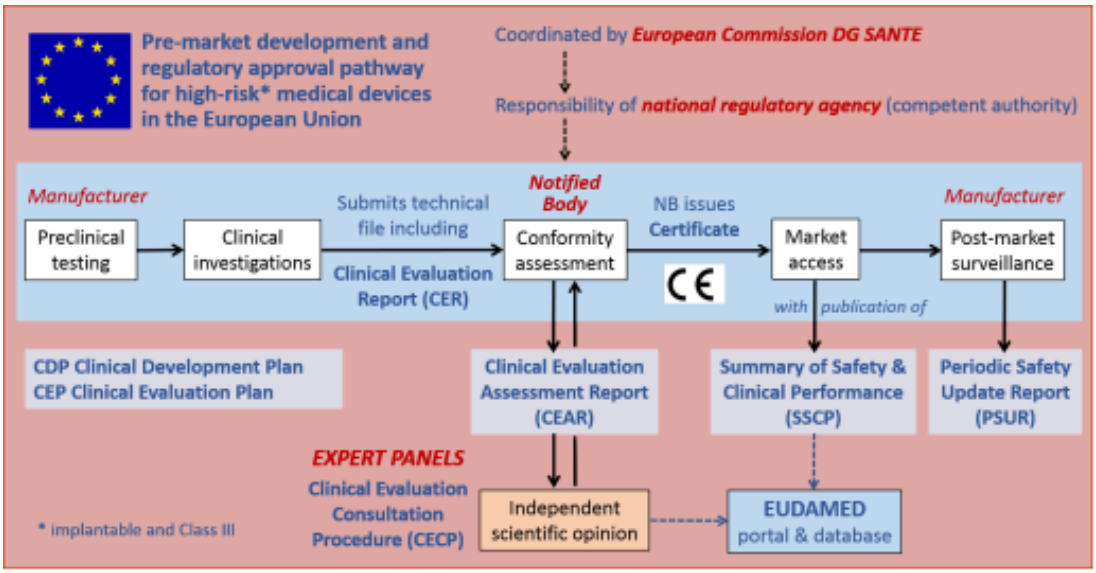


Figure 6. Pre-market development and regulatory approval pathway of high-risk medical devices in the European union

The new European Union law governing the regulatory approval of medical devices took effect from May 2021 in this report from the Regulatory Affairs Committee of the ESC they highlighted the changes which took place and the mechanism developed to provide transparency by summarizing the main safety and performance aspects of devices and the outcomes of the clinical evaluation in a document that should be publicly available having this background in mind.[Figure 6] Clinical evaluations of different Devices one of the devices failed after being for considerable time available for clinical use and the other is referring to a very successful class of devices which changed the landscape of Class c-based interventions. (17)

5.2 Case Study 2: Evaluation of Bioresorbable Scaffolds

The European Association of Percutaneous Coronary Interventions (EAPCI) task force evaluated and established a comprehensive list of all drug-loading coronary stents that had received CE mark back to that day as depicted in Figure7. The group performed a systematic review of the literature of all published randomized clinical trials. The device that was removed from the market after being available for clinical use for a considerable amount of time was made by reservable scaffolds.

Evaluated coronary artery stents and offered suggestions for a new coronary stent regulation procedure; they also found over 150 randomized trials with coronary stents bearing the CE Mark. In order to strike a balance between preserving patient safety and avoiding needless delays in the release of Innova Technologies for clinical use, the task force recommended several crucial milestones in the clinical development strategy for the evaluation of coronary devices back in the day. (18)

After few years, the ESC ABCI task group organized a dedicated report on the class of devices known as ‘Bioresorbable Scaffolds’. The scaffold were introduced as a novel technology with potential advantages over the metallic Coronary stents.

It was hypothesized that scaffolds might:

- address late stent failure
- potentially eliminate the risk of late adverse stent related events and
- contribute to the restoration of physiological vasomotion

In the ESC –EAPCI report five different devices were identified as shown in depicted in Table 1 and the task force provide recommendations concerning the clinical

use of the scaffolds and recommendations for preclinical and clinical evaluation before approval of these devices.

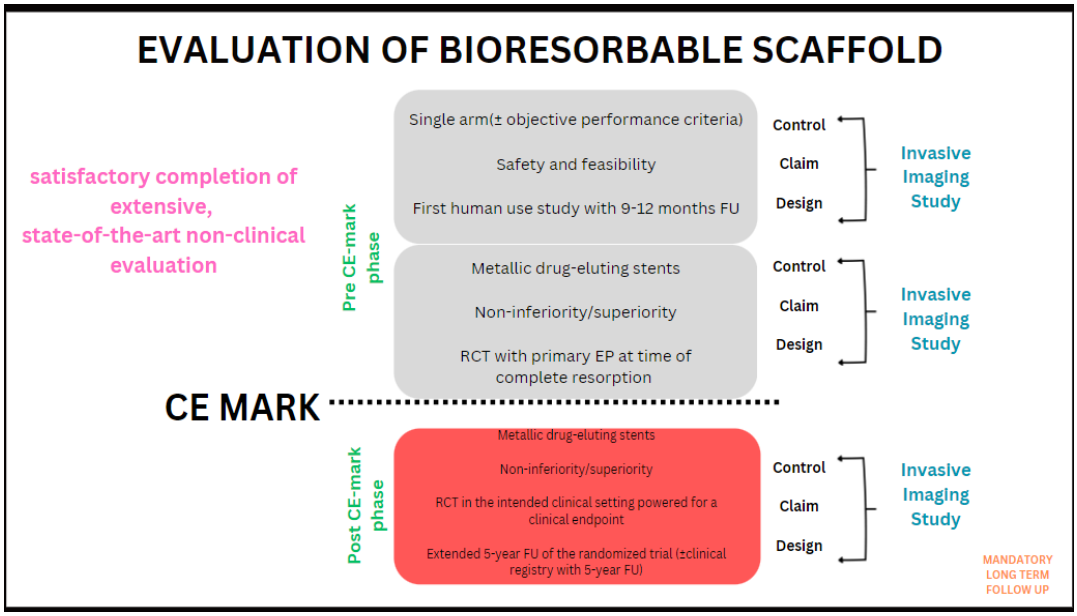
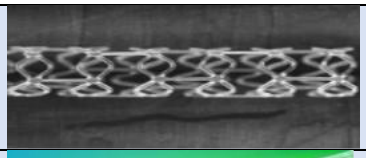
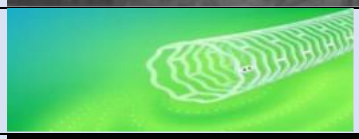
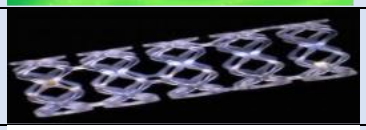
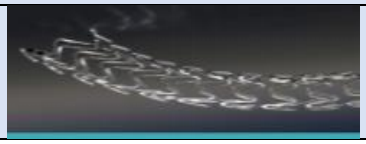


Figure 7. Evaluation of bioresorbable scaffolds-a systematic review of 158 RCT's

Table 1. Different types of scaffolds

PLLA	A Absorb	
	B DESolve	
	C ART	
Desaminotyrosine polycarbonate	D Fantom	
Magnesium	E Magmaris	

They also highlighted that only one device at the time of the absorbable vascular scaffold had published data from randomized clinal trials and this data showed inferior outcomes compared to Conventional drug eluting stents for this reason the conclusion was that scaffold should not be prepared/ preferred over Drug eluting stents in clinical practice for the only device with evidence from randomized trials the absorbable scaffold.

They also evaluated how a stepwise approach of monitoring and quantitative synthesis of the evidence over time could potentially identify the time point when firm evidence for safety concerns even of this relative rare outcome becomes available in that case eight randomized Trials of more than 8,000 were included and as you can appreciate in this Forest of cumulative meta-analysis CE Mark was granted in January 2011 without any evidence from clinical trials but with evidence suggestive of harm related to being already publicly available before FDA approval in July 2016 the risk of the evidence after FDA approval increased considerably the Precision of the estimates over time finally the device was withdrawn in September 2017. (19)

5.3 Case Study 3: Evolution of Tavi

On the other side there are successful classes of cardiovascular devices and one of them is definitely the "Tavi- Transcatheter Aortic Valve Implantation" the evolution of Valvular Heart Disease patients care was

either surgical or percutaneous especially over the last 50 years as seen in Figure 8.

Historical background- VHD interventions

TAVI devices trials have been a very good example of natural progression from superiority trials to non-inferiority and accumulation of successful evidences as shown in Figure 9. It is an example which shows how this transition can safety take place while it's moving at the same time to broader populations when the trials are appropriately designed even in the scenario of an Innovative alternative treatment.

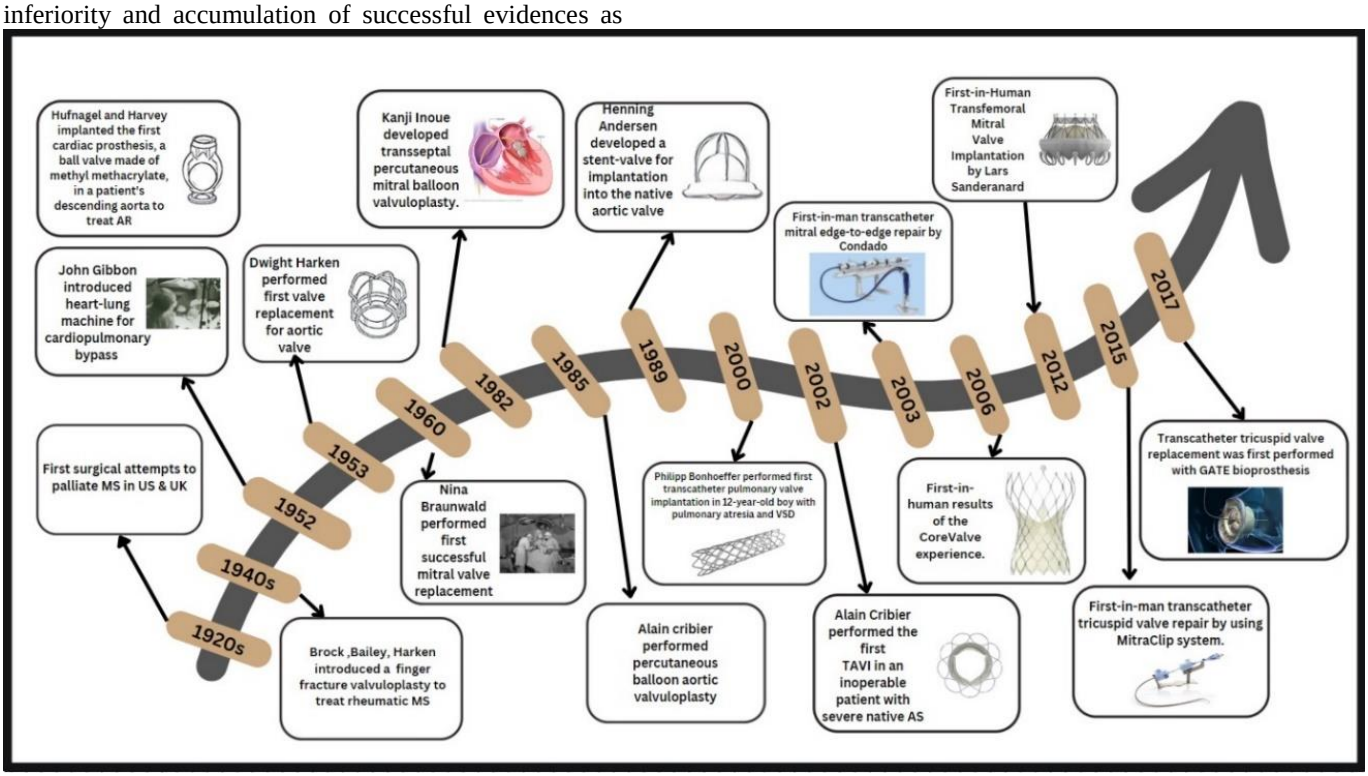


Figure 8. Evolution of TAVI devices

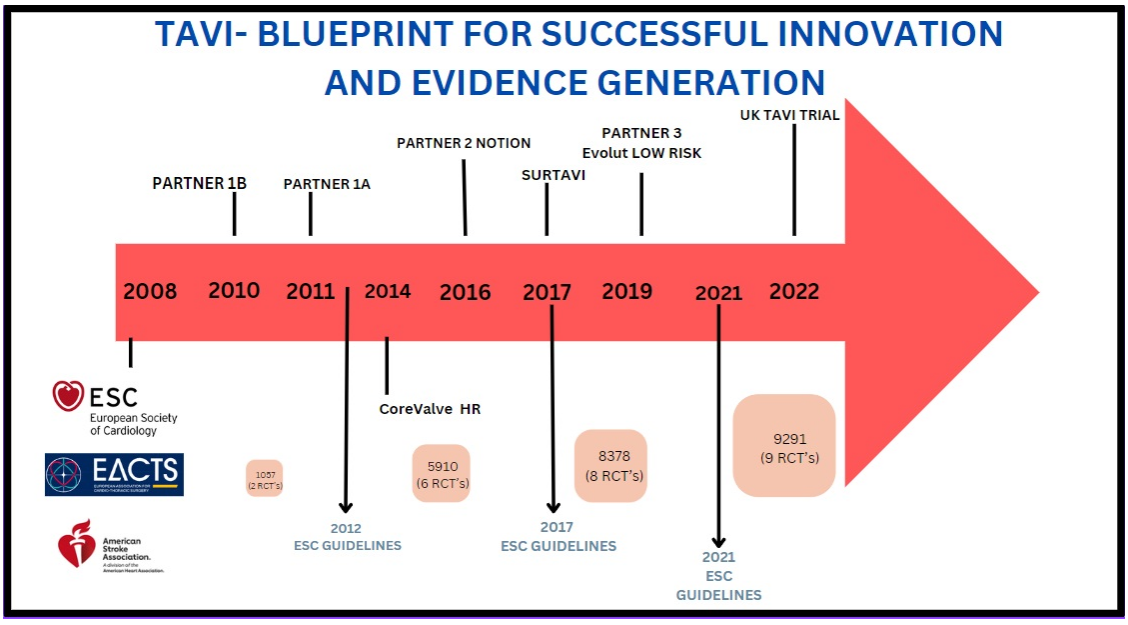


Figure 9. Innovation and evidence generation of TAVI devices

The accumulation of evidence over time illustrate safe transition moving from high risk candidates to a broader potential population when at the same time superiority trials are followed by non-inferiority trials this solid evidence around TAVI over a decade now has been translated into an upgrade of the corresponding recommendations in the clinical practice guidelines and at the same time this rapid evolution in the specific field requires equational updates of what we should consider appropriate clinical head points.

For trans surgical Aortic valve clinical trials indicative of the progress in the specific field Tavi changed the field of cardiovascular medical devices dramatically and there's no doubt that Tavi fuels the transcatheter valve therapies beyond the aortic valve and actually it serve as a blueprint

for evidence-based evaluation of device in this field of cardiovascular medicine having all the heterogeneous facts in mind it is clear that there is a need for better understanding of the evidence used in the past to assess high-risk medical device before and after CE Marking.

5.4 Case Study 4: High Risk Diabetic Devices Regulation/ Recommendation

Over the past three decades, there has been an exponential increase in the usage of medical devices for diabetes. Regulating the safety, efficacy, and dependability of these devices has sadly remained subpar during this time, despite the numerous items that have become available.

It is now more than 30 years since the use of home blood-glucose monitoring in insulin-treated patients with diabetes became widespread. At about the same time as this practice was introduced, continuous subcutaneous insulin infusion (CSII) was first described in patients with type 1 diabetes:4 early insulin pumps were simple syringe drivers without software control or wireless connectivity, and their use was initially mainly experimental. In complete contrast to the situation then, in 2013, virtually every insulin-treated patient and many non-insulins treated patients with type 2 diabetes rely on home blood-glucose monitoring to optimize blood glucose control, and tens of thousands of patients with type 1 diabetes regularly use CSII for insulin delivery. Modern devices, including insulin pumps and continuous glucose monitoring (CGM), in contrast to earlier devices, use complex sophisticated technology often with inbuilt software and calculators, wireless connectivity, and are in widespread clinical use

Devices used in diabetes are either Class 2A (e.g., home blood-glucose monitoring, CGM, home blood-pressure monitors) or Class 2B (e.g., insulin infusion pumps)

A company wanting to register a new device, such as a home blood-glucose monitoring meter or an insulin pump, can choose any notified body to which they present a dossier of evidence and pay a fee. Once approved by a notified body, CE mark is given and the device can then be marketed across the EU.

There are no agreed-upon post-marketing surveillance protocols in place by national or European health authorities, nor are there any prerequisites for independent testing of novel devices. A series of high-profile failures of medical devices used in clinical practice in recent years led by the European Association for the Study of Diabetes (EASD) to express serious concern about the registration and regulation of medical devices in Europe In view of the many problems with the regulation of medical devices used in diabetes, the EASD has organized a series of meetings of interested parties to review the current situation and propose how this situation might be improved. (1)

Classes of Diabetic Medical Devices

The Diabetic Medical Devices are classified into various categories as shown in Table 2

Table 2. Classification of diabetic medical devices

CLAS OF DEVICE	DEVICE	MANUFACTURE	CE MARK APPROVLAL DATE
IMPLANTABLE CGM DEVICE	Implantable Eversense CGM sensor	Senseonics Inc	2016
IMPLANTABLE INSULIN PUMPS	MiniMed MIP 2007C Dia Port	Medtronic Roche	2013 2012
AUTOMATED INSULIN DELIVERY DEVICES ***Hybrid closed-loop systems***	MiniMed 670G MiniMed 770G MiniMed 780G Control-IQ Diabeloop Inreda Diabetic Omnipod 5 system	Medtronic Medtronic Medtronic Tandem Diabeloop Inreda Insulet	2018 2020 2020 2020 2018 2016 2022
Fully closed-loop system	CamAPS FX CamAPS HX	CamDiab CamDiab	2020 2020

6. Evaluation and CE marking of diabetic medical devices

All medical devices used for self-monitoring of blood glucose (BG), insulin injection, continuous subcutaneous insulin infusion, and continuous glucose monitoring in the European Union (EU) must have a Communauté Européenne (CE) mark. The approval procedure for acquiring this mark, however, differs from that of the Food and Drug Administration in the US and the European Medicines Agency in the EU for medications and in vitro diagnostic equipment, respectively. This evaluation is carried out in collaboration with the manufacturers by the notified entities engaged in the CE mark process. Their knowledge of diabetes is minimal, and they must operate a variety of medical equipment. What the EU lacks is an impartial organization that regularly and critically assesses the efficacy of diabetic treatment devices both before to and following market approval. (20)

6.1 Notified body and its role in CE marking

85/C 136/01 Council Resolution of 7 May 1985 on a New Approach to Technical Harmonization & Standards "National bodies authorized to issue marks or certificates of conformity shall be notified by each Member State to the Commission and to the other Member States." The role of notified bodies in CE marking process is seen in Figure 10

Notified body's role

- Notified bodies are searching for conformity, not nonconformance.
- Notified bodies are not permitted to offer consulting services.
- Notified authorities search for evidence of conformity by requiring manufacturers to produce factual and scientific judgments to meet the standards.
- Notified agencies cannot furnish producers with answers, excuses, or assumptions about gaps in evidence.

Figure 10. Role of notified bodies in CE marking process

7. Clinical Evaluation of Artificial Intelligence System of Medical Devices

Though few have yet to show a discernible improvement in patient care, an increasing number of AI-based clinical decision support systems are performing well in preclinical, in silico evaluation. To determine an AI system's true clinical performance at a modest scale, guarantee its safety, assess the human elements associated with its use, and prepare the way for more large-scale trials, early-stage clinical evaluation is crucial. (21)

Although there have been notable advancements in these technologies recently and a rise in the quantity of devices available, questions have been raised over the caliber of the data regarding medical AI's effectiveness. Issues have been identified with AI systems that may still be in the development stages. Lack of external validation of the systems (using the same dataset for both training and validation) is one of the concerns found; there are also not enough randomized clinical trials or multi-site evaluations, which could cause overestimations of diagnosis accuracy. These flaws mean that the developers of the tested AI systems may have exaggerated the systems' safety and performance. The academic community has been developing guidelines for the different kinds of studies where AI systems are created and tested in response to these problems. On May 26, 2021, a new Medical Device Regulation (MDR) pertaining to medical AI devices went into effect in Europe. A few writers have looked at how the MDR affects medical AI devices and what needs to be done to comply with the regulations.

Numerous gadgets that were classified as low risk under the MDD will suddenly be classified as high risk. While Rules 9, 10, 12, and 13 may potentially be applicable, Rule 11 of the MDR deals specifically with the risk rating of software. This software risk classification follows the International Medical Device Regulators Forum's methodology, which takes into account the importance of the data from the SaMD [Software as a Medical Device] for the healthcare decision as well as the current status of the healthcare environment. These two variables are dependent on the manufacturer's intended usage, not the technology employed. Rule 11 in the MDR states that:

Software meant to give information for diagnosis or therapeutic purposes is categorized as class II a, unless the decisions made by the user have the potential to:

- result in death or an irreversible decline in a person's health, in which case it falls into class III;
- result in a serious decline in a person's health or a surgical intervention, in which case it falls into class IIb

Software designed to track physiological processes is categorized as class II a, unless it is meant to track vital physiological parameters and the variations in those parameters could put the patient in immediate danger. In that case, the software is categorized as class IIb. Class I software refers to all other software. (MDR Annex VIII, Rule 11, Section 6.3) (9)

8. EU initiatives on governance of artificial intelligence

OM / Al Watch at the JRC in Seville; 2018 / COM / DG CNECT / High-Level Expert Group; 2020 / EP / STOA / Centre for Al (CAI); 2021 / COM / Proposed Regulation on Al (2021/0106)

8.1 Some relevant EU legislation

(EU) 2016/679 / General Data Protection Regulation (GDPR), (EU) 2022/868 / Data Governance Act (DGA), COM (2022) 197 / Proposal for a European Health Data Space (EHDS), COM (2022) 68 / Proposal for a Data Act, EP Resolution 20.10.2020 on IP rights for development of Al technologies, Directive 85/374/EEC of 25 July 1985 on liability for defective products, COM (2022) 496 / Proposal for an Al Liability Directive, Network and Information Security Directive (NIS Directive) of 2016 [cybersecurity]

8.2 General conclusions from the CORE-MD review of medical Al systems

The European and global institutions and organizations that are involved in development for regulations in the medical AI system are shown in Figure 11.

* Regulatory efforts should concentrate on gaps in advice, or challenges unique to Al devices:

- specific methodologies for clinical investigations related to particular defined levels of risk

- how to assure use of Al system only for individuals for whom it has been validated

- how to approve iterative changes in software that may be self-learning

- how to conduct appropriate post-market surveillance

Figure 11. Overview of European and global institutions and organizations in the regulatory initiatives for AI

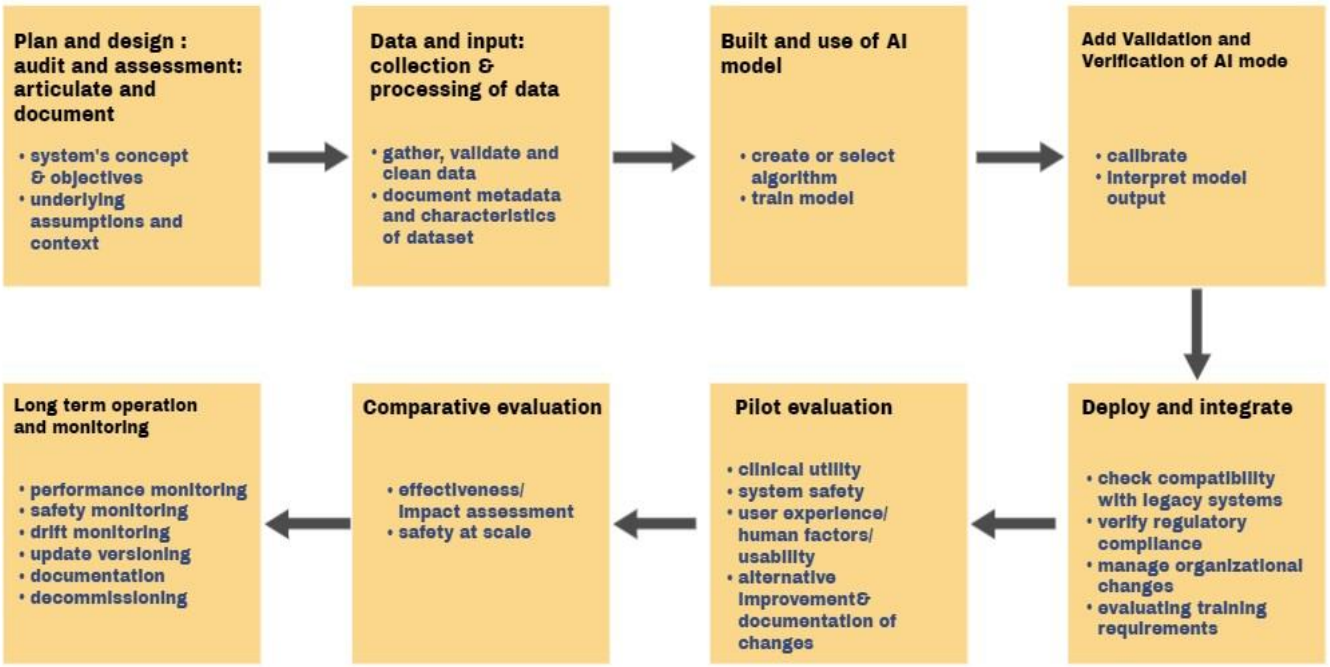


Figure 12. Requirements through AI life cycle

8.3 Requirements through AI life cycle

The requirements and the various steps involved in the AI life cycle is shown in Figure 12. Ensure transparency and explainability. Al should be understandable to developers, users and regulators

Transparency

- sufficient information published or documented before the design and deployment
- To facilitate meaningful public discussion and consultation on the best ways to use and design it.

Explainable

- information should be tailored, according to the capacity of those to whom the explanation is directed
- possible trade-off between full explainability of an Al algorithm (at the cost of accuracy) and improved accuracy (at the costs of explainability)

9. Conclusion

A prespecified protocol for this study is publicly available in Prosper registry and CORE MD website, well validated approaches to retrieve reports of Interest following the Prisma recommendations and use of device specific search algorithms for studies of prospective design are given. The information is summarized on study design, populations, interventions and outcomes. The analysis was done on study level and followed data driven approach to evaluate differences in the distributions of characteristics before and after CE mark. And later Predefined seven groups of class III cardiovascular devices of which 71 devices were put on the European Market.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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