CORE-MD

Coordinating Research and Evidence for Medical Devices

Regulatory science for high-risk medical devices in the EU

Translating expert knowledge into advice for EU regulatory guidance, and building expertise in regulatory science in the clinical community

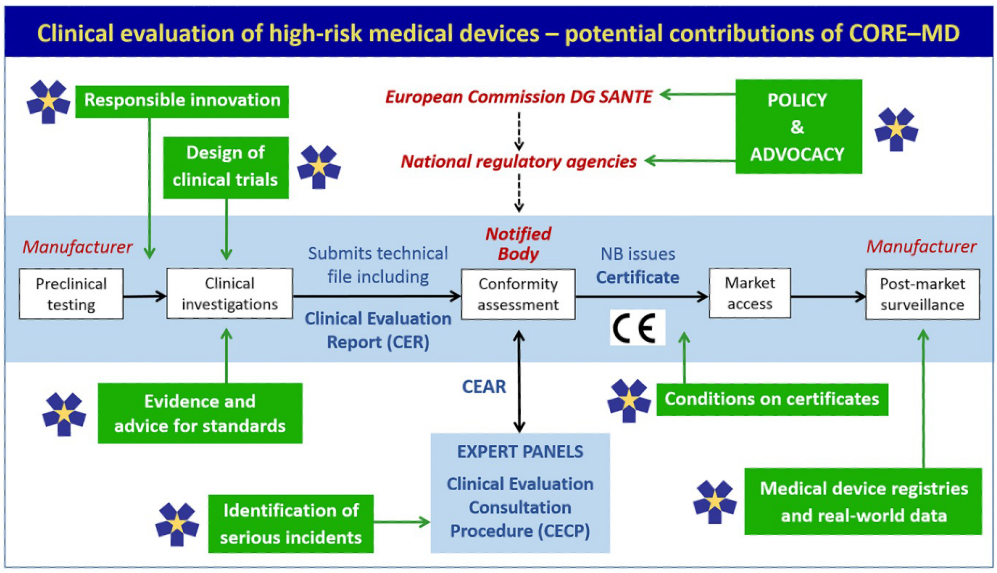
The Treaty on the Functioning of the European Union states that the European Commission and Member States can take joint measures "setting high standards of quality and safety for medicinal products and devices for medical use" when it is necessary for a high level of human health protection (Article 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. Its approval was followed by a significant increase in the workload of the Medical Technology Unit in the Directorate General for Health and Food Safety of the European Commission (DG SANTE) that is responsible for coordinating the implementation of the MDR, but the increase in manpower that was recommended in the Impact Assessment did not occur.

A Horizon 2020 research call [SC1-HCO-18-2020] therefore requested proposals to develop methodological approaches for the improved clinical investigation and evaluation 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.

There were 4 main objectives:

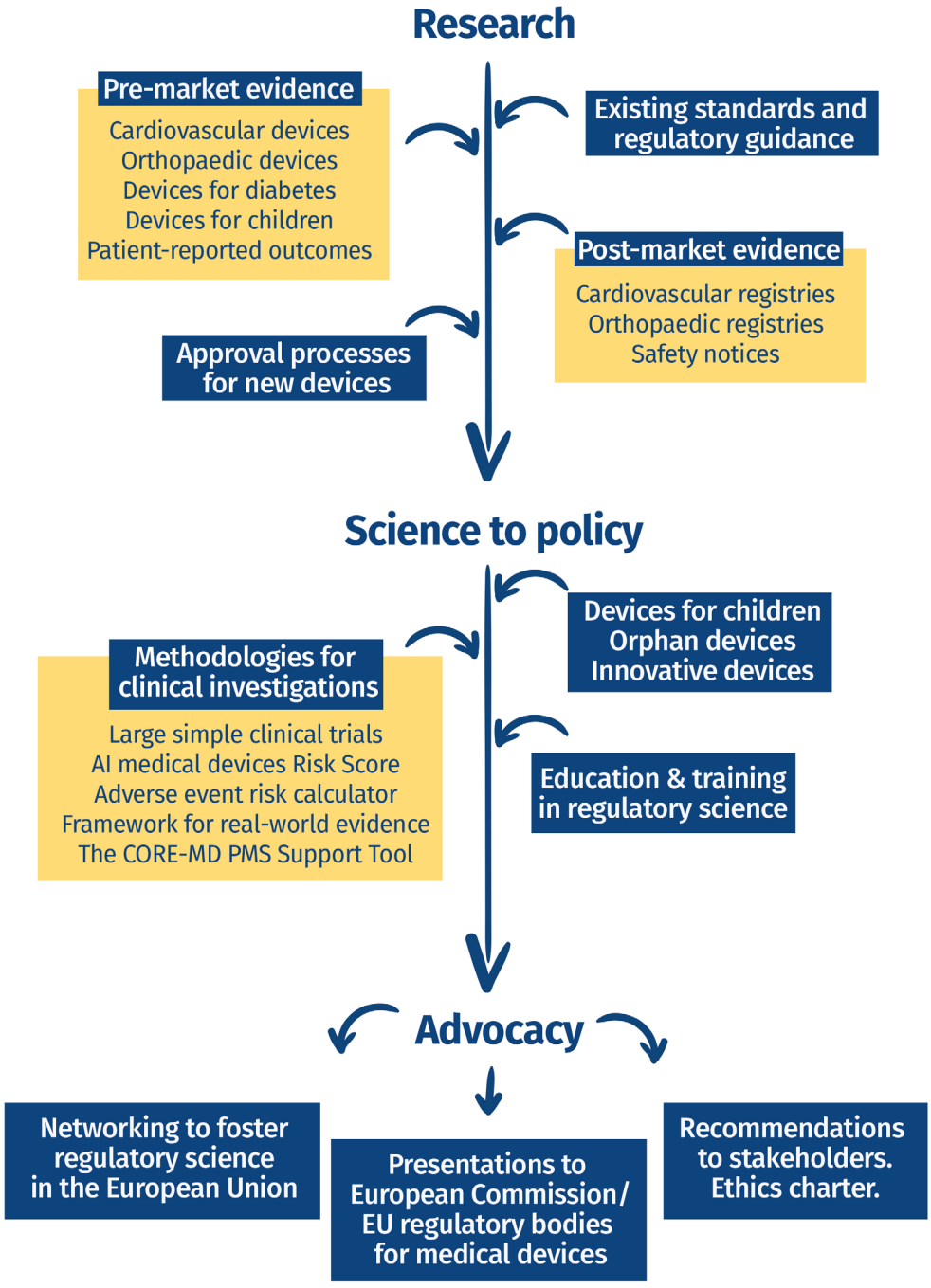
- To investigate the methodologies of clinical investigations that have been used to evaluate high-risk cardiovascular, orthopaedic, and diabetic medical devices.
- To review and recommend alternative designs of clinical studies that can provide high-quality clinical evidence for new high-risk medical 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 centres and across medical specialties, with notified bodies, regulators, manufacturers, health technology assessment bodies, and patients.



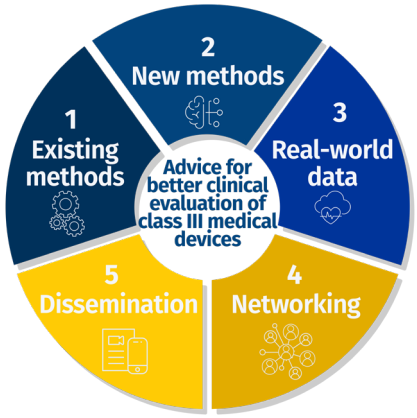
Published protocol: Fraser AG et al; CORE-MD Investigators. Improved clinical investigation and evaluation of high-risk medical devices: the rationale and objectives of CORE-MD (Coordinating Research and Evidence for Medical Devices). Eur Heart J Qual Care Clin Outcomes. 2022; 8: 249–258.

The CORE–MD Journey, April 2021 to March 2024

The premise of CORE–MD was that regulatory policy concerning medical devices should be based on scientific and clinical evidence. The primary focus concerned cardiovascular and orthopaedic devices, since together they account for >50% of all high-risk implanted medical devices, as well as devices for diabetes care.



INDEX – Summaries of work packages and tasks



What evidence is published for high-risk cardiovascular devices in Europe?

University of Bern and the Royal College of Surgeons of Ireland

Objective

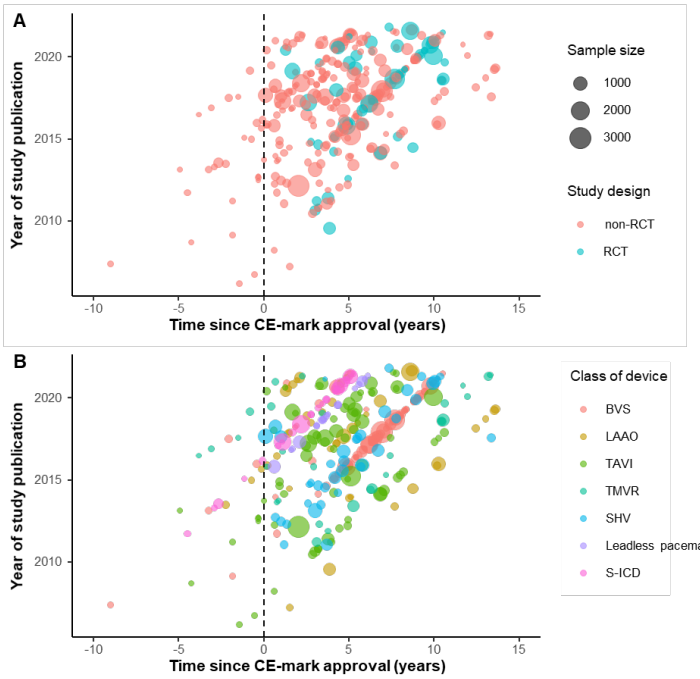
A systematic review of clinical evidence and study methodologies for specific implantable cardiovascular devices, published before and after CE-mark approval.

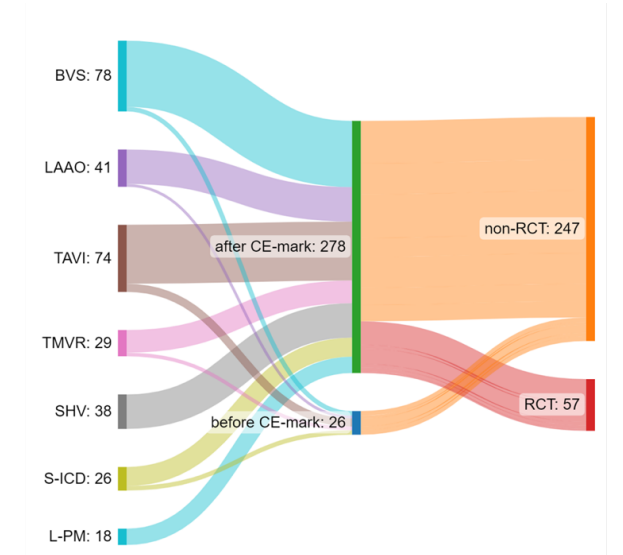
Description

We evaluated 71 high-risk cardiovascular devices from 7 selected types, and identified 308 prospective studies that had enrolled 97,886 individuals over 20 years (2000–2021).

Findings

- Only 9% of the studies were published before the devices were marketed.
- None of the reviewed devices had a randomized clinical trial published before the date of CE-marking.
- No clinical trial was found for 30% of the pre-specified devices.
- 19% of all the studies were randomized controlled trials.
- Median sample sizes were 100 for non-randomized and 304 for randomized trials.
- Power calculations were reported for 6% and 84% of those studies, respectively.
- The mean follow-up duration was 13 months.
- Risk of bias could be assessed in 17 out of the 251 non-randomized studies, of which 73% were judged to be at critical risk





BVS bioresorbable vascular scaffolds; LAAOs left atrial appendage occlusion devices; TAVI transcatheter aortic valve implantation; TMVR transcatheter mitral valve repair/replacement; SHV surgical heart valve replacement; S-ICD subcutaneous implantable cardioverter-defibrillator; L-PM leadless pacemakers.

Siontis GCM et al. Quality and transparency of evidence for implantable cardiovascular medical devices assessed by the CORE-MD consortium. Eur Heart J. 2024; 45: 161–177.

What evidence is published for high-risk orthopaedic devices in Europe?

University of Oxford and Geneva University Hospitals

Objective

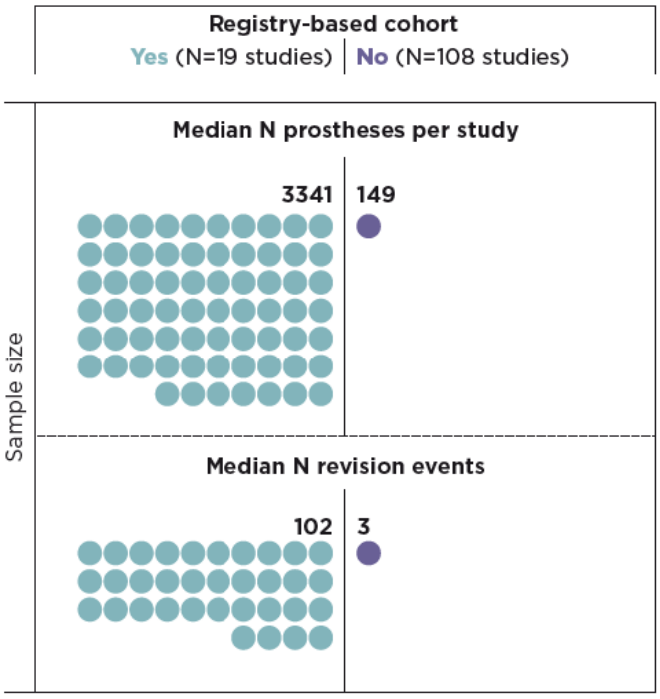
A systematic review of peer-reviewed clinical investigations for selected hip and knee arthroplasty implants, published before and after CE-mark approval.

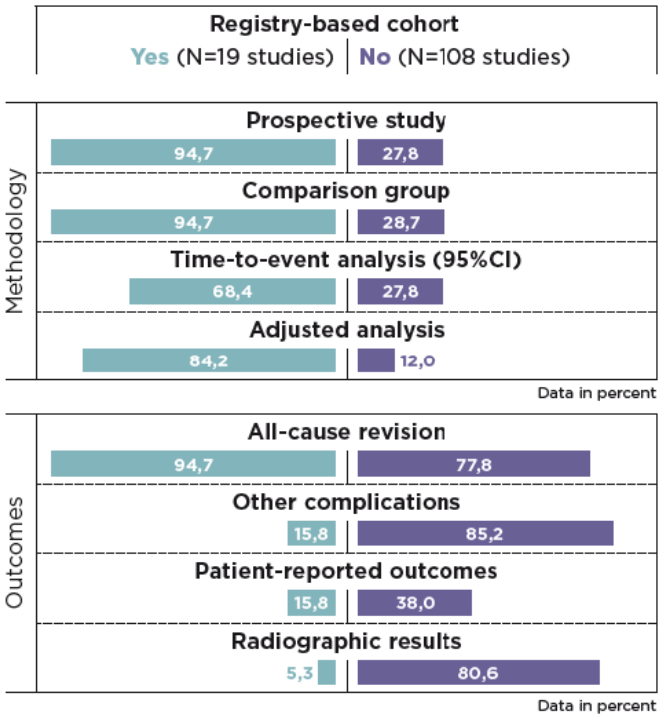
Description

- We identified 151 retrospective or prospective studies that had evaluated 30 randomly-selected orthopaedic implants (10 hip stems, 10 hip cups, and 10 knee systems), from 10 years before and up to 20 years after regulatory approval (between 1995 and 2021).
- 1,814,953 subjects had been enrolled in observational and randomized studies.

Findings

- No studies were published before the dates of regulatory approval (CE-marking).
- The median interval between first recruitment and publication of results was 10 years.
- 27% of the devices had no peer-reviewed publication up to 20 years after approval.
- 9% of the identified studies were randomized controlled trials; 72% were cohort studies.
- For 33% of implants we found no comparative study, and for 40% no prospective study.
- The median number of implants in a study was 139 (ranging from 1 to 27,193).
- The median duration of follow-up was 4.6 years (but highly variable).
- Sample sizes were much greater and study methodologies much better in registry-based cohort studies (figure).
- A safety concern was expressed in 5% and a potential concern in another 7% of studies.





Lübbeke A et al. Clinical investigations to evaluate high-risk orthopaedic devices: a systematic review of the peer-reviewed medical literature. EFORT Open Rev. 2023; 8: 781–791.

What evidence is published for high-risk devices for diabetes care in Europe?

Bern University Hospital

Objective

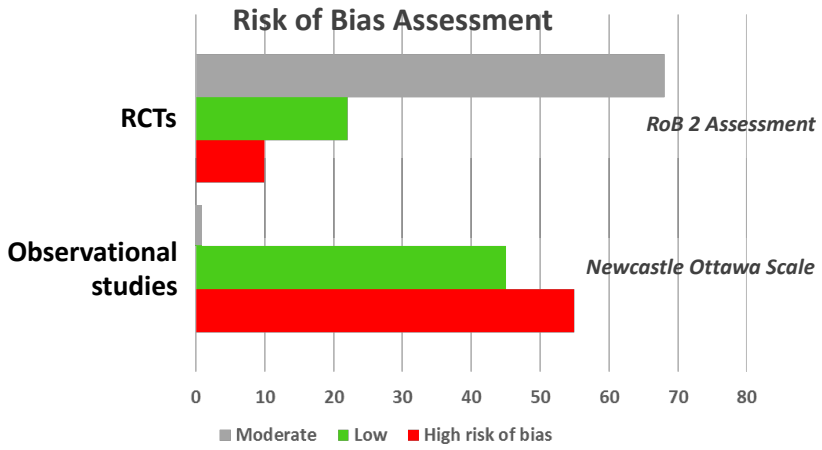
A systematic review of published observational and interventional studies evaluating the efficacy and/or safety of high-risk medical devices approved for diabetes care.

Description

We identified 110 studies published between 2009 and 2022 that had evaluated 8 automated insulin delivery systems, 2 implantable insulin pumps, and 1 implantable continuous glucose monitor, in a total of 30,059 subjects.

Findings

- 27% of studies were published before the dates of regulatory approval (CE-marking).
- 29% of the identified studies were randomized controlled trials.
- The median sample size was 52 participants.
- The median duration of follow-up was 13 weeks.
- 62% of studies compared safety outcomes.
- Risk of bias was assessed as high in 9% of RCTs and 57% of observational studies.



Bano A et al. Clinical evidence for high-risk medical devices used to manage diabetes: protocol for a systematic review and meta-analysis. BMJ Open. 2023; 13: e070672. (Results submitted for publication)

Implications of these systematic reviews

- The evidence that is publicly available from clinical investigations of high-risk medical devices before their regulatory approval and CE-marking is insufficient to enable physicians to make informed recommendations to patients of which device to use.
- Clinical trial evidence should be published when new devices are approved.
- More systematic and efficient methods are needed to evaluate the long-term safety and performance of high-risk medical devices.

What are the statistical implications of small studies with short follow-up? The CORE–MD Risk Calculator

Leiden University Medical Center

Background & Objective

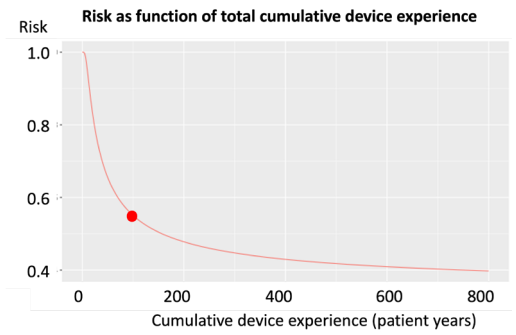
- Underpowered clinical studies have limited capacity to detect uncommon effects or complications. In consequence, unknown risks of devices may be tacitly accepted.
- As an exemplar, ISO standards for heart valves recommend 800 patient-years as the minimum cumulative experience that should be collected, before regulatory approval.
- How can regulators, healthcare professionals, and patients be informed of the implications of limited information, if it has been accepted as sufficient for approval?

Description

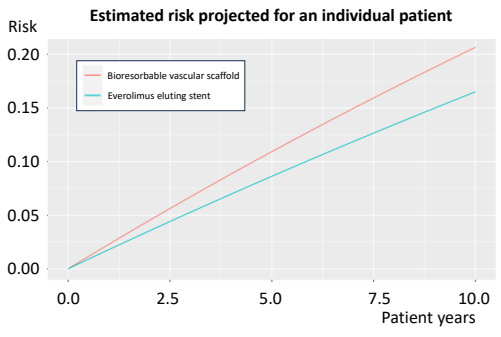
- We developed a Bayesian analysis and implemented an on-line tool that gives the user objective insight into risks that may not have been detected, when devices are approved with limited clinical experience.
- The input to the model is the cumulative total of patient-years of exposure to the investigational device, and the amount of observed (or estimated) events.
- The output is the upper limit to the risk at any given year, as a function of the cumulative device experience, given that the observed event rate is the true event rate.

This graph shows the hypothetical situation for a device with 100 patient-years of exposure and 4 events. If we collect 800 patient-years' worth of experience, with no change in the observed event rate, then we would be able to conclude with 90% certainty that a patient's 10-year risk is lower than 0.4.

The tool should help with decisions about how many patients to study, in order to achieve the desired confidence of excluding adverse events with different probabilities.



The tool was tested on a dataset of studies of bioresorbable vascular scaffolds. The graph shows the smallest risk that can be excluded with 95% probability, from the time of implantation of a BVS, compared with an approved drug-eluting stent.



The tool can be used by regulators to help decide whether to approve a device. Clinicians and patients can use it to make informed decisions on what device to implant. The tool can be accessed via:

https://jwavanegeraat.shinyapps.io/COREMD_RiskCalculatorV4/

What is the regulatory utility of patient-reported outcomes?

University of Göteborg and the European Patients' Forum

Objectives

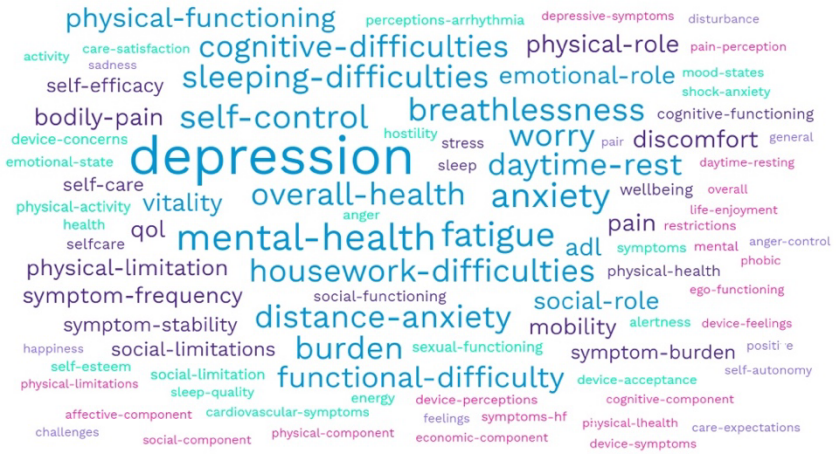
- To analyse the use of Patient-Reported Outcome Measures (PROMs) in trials, studies, and surveillance of high-risk cardiovascular, orthopaedic, and diabetic medical devices.
- To provide the perspective of patients on their high-risk medical devices.

Description

We performed a systematic literature review; and we surveyed patients' and carers' views through a Delphi study, an online survey, and discussions in focus groups.

Findings

- Many different generic and condition-specific PROMs instruments were found in this review (82 in total). Only 2 were designed to measure acceptance of a medical device.
- About 50% of the RCTs reported significant or meaningful difference in PROM values.
- Patient reporting follow-up times differ across studies; PROM completion declines after implantation. Studies were smaller and shorter when PROMs were primary outcomes.
- Many patients lack familiarity with PROMs and need clarity on how their feedback is used. There is no indication that PROM results are transmitted to patients.
- Patients want to be involved in the co-design of devices and explanatory material, and they seek effective communication channels with manufacturers.
- Key concerns to patients are device safety, performance, functions, and how the device fits into their lifestyle. Outcome variables by frequency for the cardiac PROMs that had been used in the published medical device studies are shown in the word cloud:



❖ More research is needed if PROMs are to be made more relevant for medical device regulators, and if their use is to be expanded to inform the development and post-market surveillance of high-risk devices. Thresholds for minimum clinically important differences (MCID) need to be established.

Chaplin J et al. An integrative systematic review of patient reported outcome measures (PROMs) used to evaluate orthopedic, cardiovascular and diabetes high risk implantable medical devices.

[protocol] https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022344424

Published guidance and expert recommendations for clinical investigations

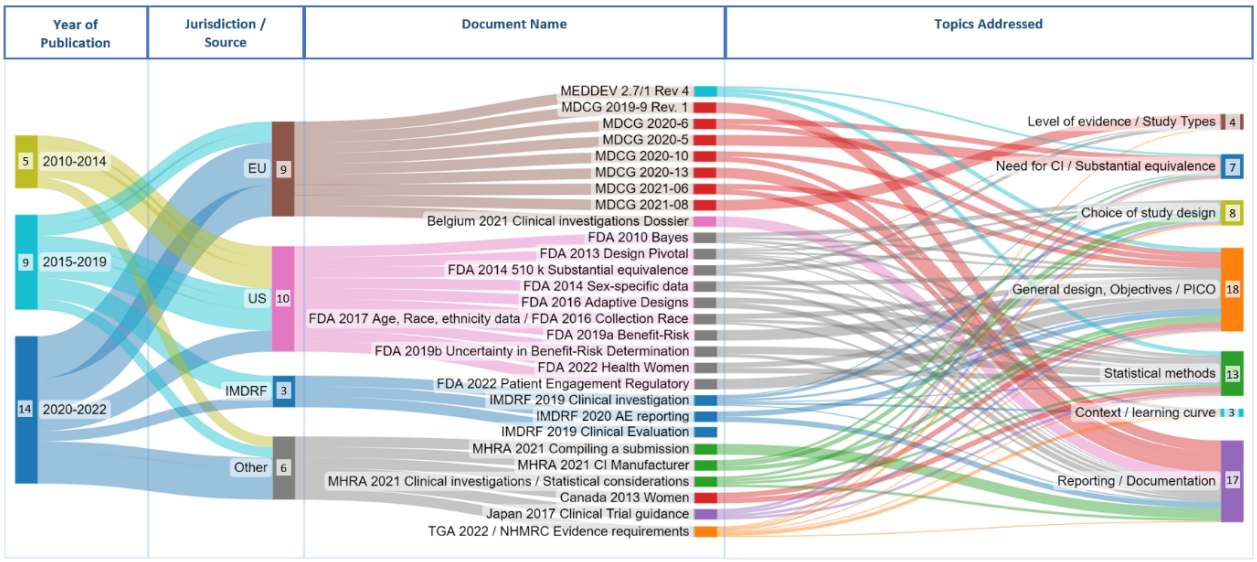
UMIT Tirol – University for Health Sciences and Technology, with Dutch National Institute for Public Health and the Environment

Objective

To systematically identify and analyse recommendations in regulatory guidance and international standards, concerning study designs for high-risk medical devices.

Description

We included 30 documents published since 2000 by regulatory authorities of high-income countries, including 3 from the International Medical Device Regulators Forum (IMDRF); 4 expert consensus statements from research consortia; and 12 International Organization for Standardization (ISO) standards (9 for cardiovascular devices):



Findings

- There is limited transparency about the processes used to develop recommendations.
- Systematic and detailed guidance is available from regulators on study designs for high-risk medical devices – regarding level of evidence, need for a clinical investigation, choice of study design, general design issues, the PICO criteria [Population, Intervention, Comparator, Outcome], and statistical methods, but this guidance comes mainly from the U.S. Food and Drug Administration.
- 8 EU documents included in this review (from the Medical Device Coordination Group) were concerned predominantly with reporting templates and documentation.
- Two regulatory jurisdictions (FDA, USA; and the Therapeutic Goods Administration in Australia) publish recommendations for a hierarchy of study designs.
- A practice-oriented analysis may identify gaps where further regulatory guidance on study design would be helpful.

❖ From the perspective of the European regulatory system under the MDR, there is too little substantive guidance on evidence standards for the design of confirmatory clinical studies for high-risk medical devices.

Schnell-Inderst P et al. Study design recommendations in guidance documents for high-risk medical devices. A systematic review. [Protocol] https://doi.org/10.17605/OSF.IO/3MF7V

Providing clinical evidence during the early development of high-risk medical devices, for regulatory submissions in the EU

University of Oxford

Objective

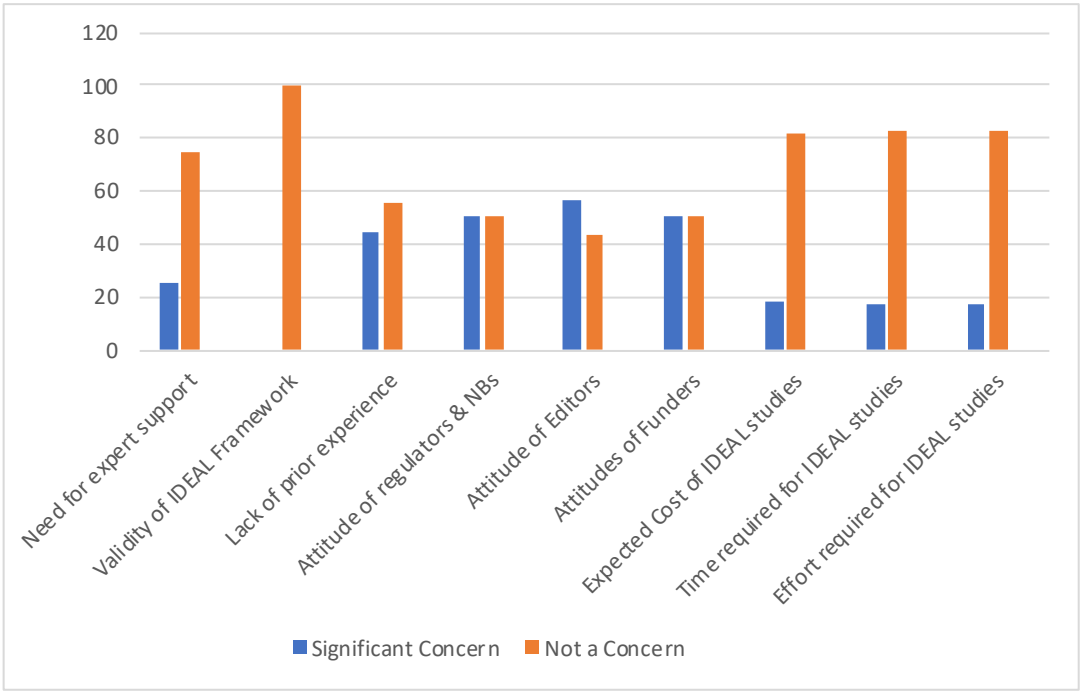
To understand and analyse the impact of the EU Medical Device Regulation (MDR) on the early clinical evaluation of new high-risk medical devices, through a series of case studies involving innovators with the IDEAL Collaboration, to prepare clinical evidence plans and to study facilitators and barriers to their widespread adoption.

Description

- An exploratory study of the feasibility and utility of the IDEAL recommendations when developing evidence for innovative medical devices within the framework of the MDR.
- Detailed semi-structured interviews with developers of new high-risk medical devices.

Findings

- Our appeals for innovators to work with the IDEAL Collaboration resulted in 22 expressions of interest, 12 from enquiries distributed via CORE-MD partner organisations and 10 from advertisement on the IDEAL website.
- The interviews identified potential benefits of adopting IDEAL for a staged approach to developing evidence for regulatory submission, but a major obstacle was imposed by lack of transparency about what the Notified Bodies and regulators would find acceptable. The chart shows what were perceived to be the major barriers:



- Only one of the 12 innovator groups from the CORE-MD partners who discussed collaboration, used an IDEAL format study in their submission for regulatory approval.
- The inability of innovators to discuss with Notified Bodies what types of studies would be acceptable effectively locks methodological innovation out, and is likely to have adverse consequences in terms of both competitiveness and safety for the EU system.

New designs for randomised trials and studies of high-risk medical devices

Universities of Uppsala and Oxford

Objective

Well-designed and accurately conducted randomized controlled trials (RCTs) contribute excellent evidence for the approval of high-risk medical devices, but barriers to their conduct have emerged, such as high costs related to complexity in governance. This task explored more efficient methodologies for obtaining high-quality evidence.

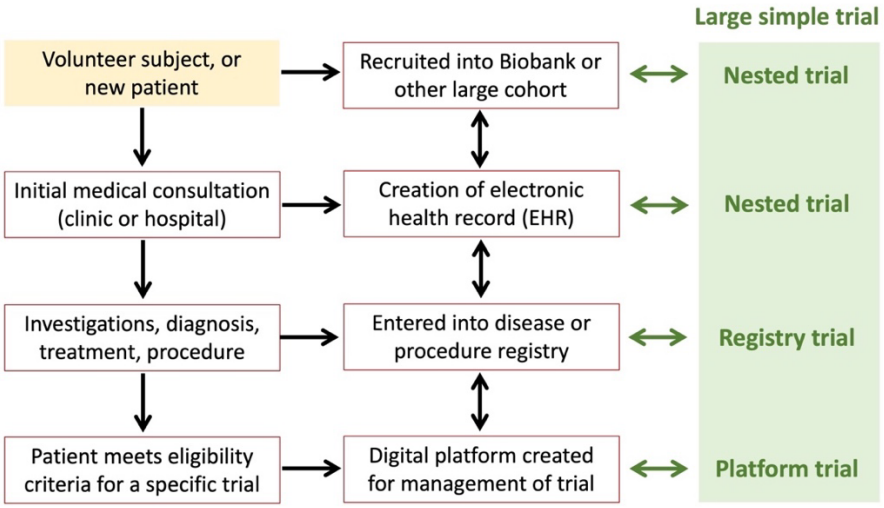
Description

Members of the CORE–MD consortium have pioneered the design and conduct of large, simple RCTs of drugs and medical devices (especially the RECOVERY and TASTE trials), and coordinated the Good Clinical Trials Collaborative. A joint review and workshop were conducted to identify the basic principles and to summarise the most important features of large simple RCTs, in order to foster their wider adoption.

A hierarchy or matrix of study designs and methodologies was proposed.

Findings

- Large simple RCTs of high-risk medical devices are feasible and can provide robust data. Their conduct may be streamlined using modern IT infrastructure and technology.
- RCTs need to be efficient in order to ensure that adequate numbers (and ideally, diversity) of patients are enrolled, and to get reliable answers to their clinical questions.
- Use of registries, platforms or other methods can help achieve these goals by minimising additional work for patients and doctors e.g. for randomisation and by embedding the routine collection of data within an electronic health record:



- The conduct of RCTs of high-risk medical devices should be supported more strongly and for some devices and at certain life-cycle stages required by regulations.

Buccheri S et al. Large simple randomized controlled trials – from drugs to medical devices. Lessons from recent experience. Submitted for publication.

Recommendations for the clinical evaluation of artificial intelligence and standalone software in medical devices: the CORE–MD AI Risk Score

KU Leuven, with support from COCIR

Objective

To propose recommendations as a basis for developing regulatory guidance on the clinical evaluation of artificial intelligence (AI) and standalone software in medical devices – with a focus on high-risk applications of machine learning and artificial intelligence algorithms, before and after their approval and implementation for patients.

Description

- We reviewed regulatory initiatives and agreed common definitions, in task group and plenary meetings of the CORE-MD consortium.
- We reviewed existing ethical, legal, and clinical guidelines and consensus statements, to define guiding principles for the clinical evaluation of AI medical device software (MDSW).
- Consultations on our draft proposals were held with EU regulators at the Clinical Investigation and Evaluation (CIE) and New and Emerging Technologies (NET) Working Groups of the Medical Device Coordination Group (MDCG) of the European Commission.
- The final policy document with practical recommendations was developed and refined by consulting 33 invited experts who participated in a two-stage Delphi process.

Findings and proposals

- We found a plethora of definitions, guidance documents, and ongoing regulatory initiatives relating to possible applications of AI in medicine. The principal governmental bodies, international agencies, and standards organisations are listed in this figure:

- 2017 IMDRF guidance on (general) MDSW recommended higher requirements for clinical evaluation and evidence of benefit, before regulatory approval, according firstly to the function of the software (ranging from informing for a non-serious condition, to when it treats or diagnoses in a critical condition) and secondly to the consequences for the health of a patient from an erroneous output from the MDSW (ranging from none, to catastrophic). We consider those 2 criteria together in a 'Clinical Performance Score'.

- The CORE–MD task group considered that additional factors should be taken into account when determining the need for extended clinical evaluation of *artificial intelligence* MDSW. These are described in a 'Valid Clinical Association Score' and a 'Technical Performance Score'. Together, assessing the components of the 3 scores could standardise regulatory review of all stages in the development of AI MDSW:

Clinical Performance Score	**CPS**	**Need for extended *pre-market* clinical evaluation if :**
Type of disease, condition, disability, healthcare situation: risk for patient **Non-serious / serious / critical**	**1 / 2 / 3**	
Significance of information: use in clinical flow **Inform / drive / diagnose or treat**	**1 / 2 / 3**	**CPS subtotal ≥ 5**
Technical Performance Score	**TPS**	
Extent of validation and testing Broad, external / narrow, external / internal **Strong / moderate / weak**	**1 / 2 / 3**	**CPS + TPS ≥ 6**
Valid Clinical Association Score	**VCAS**	
Transparency and oversight **Easy / difficult / impossible**	**1 / 2 / 3**	**CPS + TPS + VCAS ≥ 8**

Lower level of *pre-market* clinical evaluation if : CPS + TPS + VCAS total score ≤ 7

- The task group recommends that higher scores (implying greater possible risk from use in clinical practice) should mandate extended pre-market clinical evaluation, sometimes encompassing the need for a randomised trial.
- Conversely, lower scores should allow AI MDSW to be approved with less clinical evidence, shifting emphasis from the pre-release to the post-release phase but perhaps on condition that the manufacturer should undertake specified post-market clinical studies.
- The CORE–MD recommendations suggest proportionate evidence requirements for higher- and lower-scoring AI MDSW for all stages of their life-cycle, using items adapted from the list of the National Institute of Standards and Technology (NIST; in the USA).

Future directions

❖ The aim is to collaborate further with EU regulators and all stakeholders, within the framework of the MDCG, to develop a specific European guidance document on the clinical evaluation of AI MDSW.

❖ There is a pressing need for regulatory collaborations to avoid over-regulation.

❖ Identified gaps in regulatory guidance include methods to avoid 'drift' or off-label use, assuring application of an AI system only for individuals for whom it has been validated / how to approve iterative changes in software that is self-learning / and how to conduct post-market surveillance of AI MDSW.

Fraser AG et al. Artificial intelligence in medical device software and high-risk medical devices – a review of definitions, expert recommendations and regulatory initiatives. Expert Rev Med Devices. 2023; 20: 467–491.

Rademakers FE et al. A risk score to guide clinical and regulatory evaluation of artificial intelligence-based medical device software. A recommendation from the CORE–MD consortium. (submitted)

Evidence and recommendations for high-risk medical devices in children

LMU University Hospital, Munich, and European Academy of Paediatrics

Background

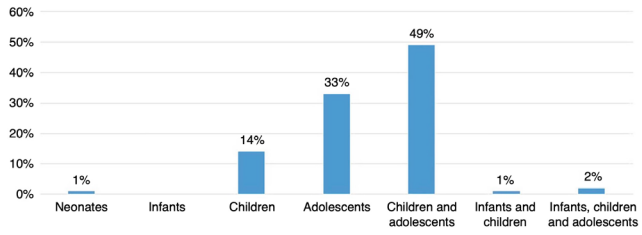
Implementation of the MDR has led to a number of orphan devices being taken off the market, when it is difficult or too costly to meet the enhanced requirements for clinical evidence. Strategies are needed urgently to protect both the patients' safety and the continued availability of essential high-risk medical devices used in children.

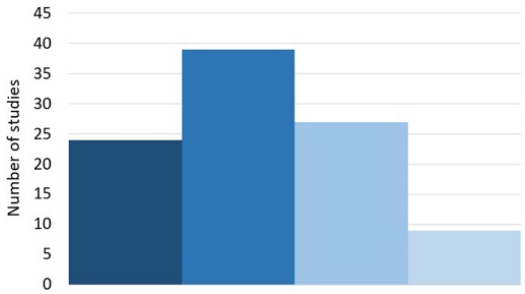
Description

- We performed a scoping review on published evidence from clinical trials of high-risk medical devices used in paediatric cardiology, diabetology, orthopaedics and surgery, in order to describe the methodologies applied.
- A workshop and a subsequent online meeting were held with 20 experts from >10 paediatric clinical subspecialties, to develop recommendations for the clinical investigation and evaluation of high-risk medical devices for children.

Findings

- 99 studies were identified and included; 38% were randomized trials.
- Very few studies enrolled infants and young children; and median sample size was 59:





- 79% of studies assessed the efficacy or effectiveness of the device; but 88% of the studies had investigated devices used to treat diabetes.

Recommendations:

- ❖ Transparency of (often limited) clinical data is essential.
- ❖ A specialist Paediatric Expert Panel needs to be established, under the MDR.
- ❖ Orphan medical device status should be designated on a case-by-case evaluation.
- ❖ The workshop recommended contextualized approaches to clinical investigations, considering the feasibility of obtaining evidence, with ethical and practical challenges.
- ❖ Competent authorities need to set realistic requirements for the level of clinical evidence to support conformity certification of devices used in children.

Guerlich K et al. Evidence from clinical trials on high-risk medical devices in children: a scoping review. Pediatr Res. 2023; Epub.

Guerlich K et al. European expert recommendations on clinical investigation and evaluation of high-risk medical devices for children. Acta Paediatr. 2023; 112: 2440–2448.

Aggregating insights from device registries and other real-world evidence

Leiden University Medical Center and Delft University of Technology

Objective

To provide insights into how registry data can be leveraged to supplement evidence from randomized controlled trials, related to the performance and safety of high-risk medical devices during post-market clinical follow-up.

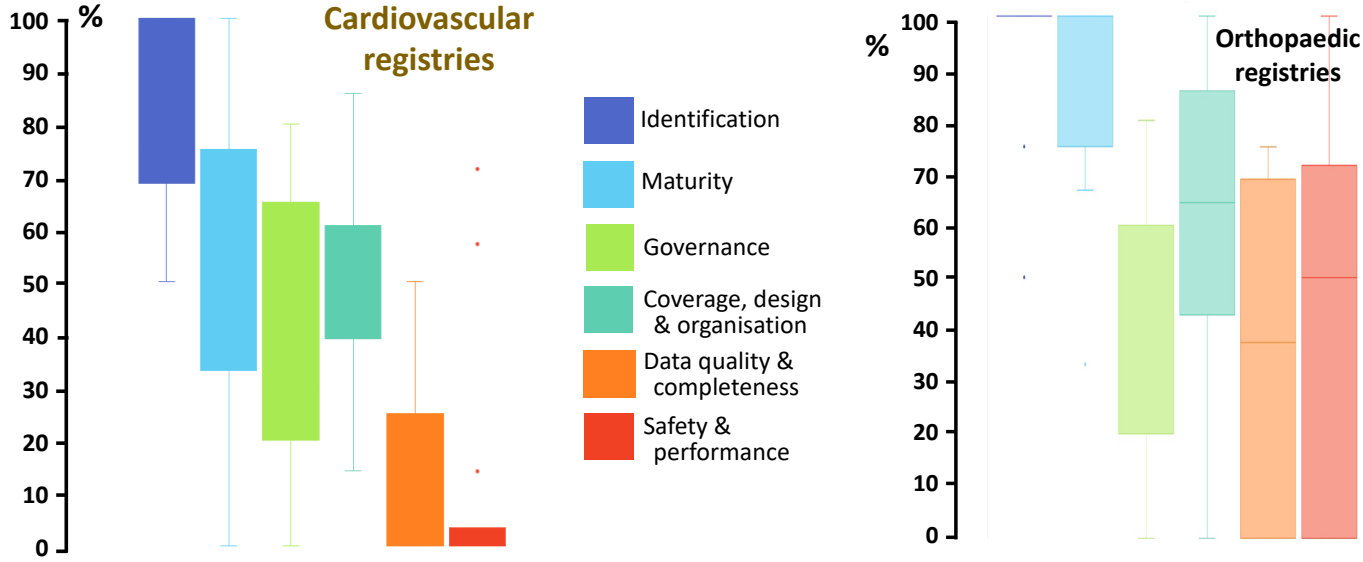
Description

Five studies were conducted, and their results applied to construct a decision framework for real-world evidence that can be used to assess the performance of high-risk medical devices:

1. A systematic review of 20 cardiovascular and 26 orthopaedic device registries in Europe, to assess reporting of structural and methodological variables that influence data quality; definitions; and endpoints included to monitor device performance.
2. Validation across 9 registries of Orthopaedic Data Evaluation Panel ratings (a benchmark system for the performance of implants) to assess whether higher-rated implants would also receive the higher rating based on evidence pooled across registries.
3. A feasibility study to combine data across orthopaedic registries, using a federated network analysis approach.
4. A feasibility study to assess if safety notices published by national competent authorities, and outliers identified by registries, signal the same or different devices.
5. A Delphi study involving 51 international experts reached consensus on a minimum dataset needed to assess the quality and analysis of registry data, suitable for the regulatory oversight of medical device performance during post-market surveillance.

Findings

1. Large heterogeneity was found between registries, across 33 items including structure and methodology, recorded outcomes, definitions of outcomes, & follow-up durations. The figure shows the percentages of items reported by cardiovascular and orthopaedic registries across 6 domains (median values 33% and 60% respectively). It would be difficult currently to collect and report comparable information for the same devices across all registries in the EU.



2. A minority of the hip cups and stems with higher ODEP ratings would receive similar ratings based on the evidence pooled from registries, indicating that the performance of implants varies across countries. Registries could validate ODEP ratings for their own country before applying the ratings to guide the selection of implants for their patients.
3. Multiple challenges hindered combining patient-level data across registries. Harmonizing data requires significant time and effort.
4. Published safety notices did not signal 26% of the outlier total knee implants identified by registries, but they also pointed to 12 implants not (yet) identified by registries. Combining various real-world data sources and methods will enhance the detection of safety signals for medical devices.
5. The Delphi consensus identified 15 items related to the quality of data and 8 items that indicate the quality of analysis; the items considered to be most important were 'completeness of procedures' and 'definition of outcomes analysed'. Medical device registries should be encouraged to report all 23 items publicly, as that would enable regulators to judge the utility of their data. A good-quality registry could then be approved as a source of reliable data for monitoring medical device performance during post-market surveillance.

Recommendations for a decision framework

- A decision framework was developed, with 'relevance' and 'reliability' as the guiding principles for deciding which post-market data can be considered trustworthy for regulatory use. The items on which consensus was achieved in the Delphi study were mapped to its domains.
- Key factors to be assessed include suitability and appropriateness of the collected data (such as broad coverage), data governance, data quality (full reporting, quality assurance, data linkage, etc.), and data analysis (including standard approaches for comparisons vs. other devices, benchmarks, or objective performance criteria; methods to adjust for confounding; and application of methods for defining outlier performance).
- This framework is likely to be valuable for manufacturers to perform the required clinical evaluation and for notified bodies to do their assessments, for competent authorities to perform their market surveillance tasks, and for clinicians and patients to establish their own insights into the real-world performance of a device.

Hoogervorst LA et al. Quality and utility of European cardiovascular and orthopaedic registries for the regulatory evaluation of medical device safety and performance across the implant lifecycle: a systematic review. Int J Health Policy Management. 2023; 12: 7648.

Hoogervorst LA et al. Validating Orthopaedic Data Evaluation Panel (ODEP) ratings across nine orthopaedic registries: better performance for total hip implants with an ODEP-rating than those without an ODEP-rating. Journal of Bone and Joint Surgery. 2024.

Development of a mashup for collecting safety notices about devices from accessible web sources: The CORE–MD PMS Support Tool

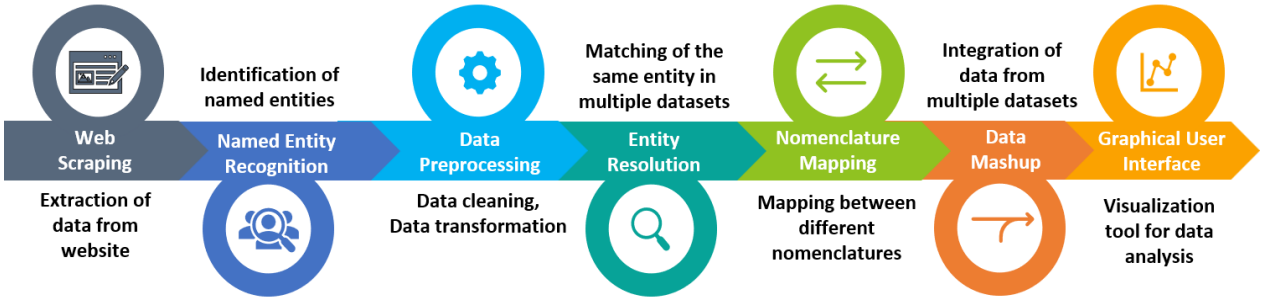
Politecnico di Milano

Objectives

- To develop a tool for automatically collecting available curated regulatory information on medical device (MD) alerts and recalls from the official websites of EU and non-EU regulatory authorities.
- To explore the feasibility of the mashup tool to capture trends in reported incidents, inform decisions by Expert Panels on the need for scrutiny within the Clinical Evaluation Consultation Procedure, and enable scientific analyses during post-market surveillance.

Description

We developed a methodological framework based on web-scraping and Natural Language Processing (NLP), tailored to each of the examined countries that have publicly available safety notices (SNs) in their websites (16 within and 5 outside the EU). Its accuracy was assessed for identifying the Manufacturer and Device name in each SN, and for attributing the EMDN code corresponding to the MD category.



Findings

A harmonized & structured database was created, with 65,809 SNs from 16 EU countries and 71,911 SNs from extra-EU countries, and with 77,669 (56%) assigned accurately to their corresponding EMDN codes. A graphical user interface (see Figure) allows multiple queries for analysing trends.

We showed the feasibility, by using NLP techniques, to overcome the complexity associated with having market vigilance information under different national jurisdictions, unstructured data across various databases, with multiple nomenclatures and languages. Sustainable development of the tool is being explored.

Ren Y et al. A novel strategy for aggregating information from notices of failures to support medical devices' post-market surveillance. Therapeutic Innovation & Regulatory Science. 2023; 57: 589–602.

Clinical evidence generation after market access

Andalusian Health Technology Assessment Unit, and TEAM-NB

Background and objectives

- Clinical evidence for new high-risk medical devices is often limited at the time when a first regulatory decision needs to be made, which confirms the crucial role for post-approval evidence in guiding decisions through a product's life cycle. EU regulations do not provide a special pathway, but Article 4.8 in Annex VII of the MDR gives notified bodies authority to grant certificates of conformity with specific conditions (such as limited indications, or requirements for post-market clinical investigations). The first objective of this task was to survey how often and for what reasons Notified Bodies (NBs) apply restrictions to the certificates that they issue.
- The second objective was to review how other regulatory authorities worldwide apply schemes for approval on the basis of coverage with evidence development.

Description

- A detailed EUSurvey was developed with 29 questions, for ***prospective*** documentation by NBs of their placing of conditions on certificates under the new MDR. It became clear that this goal was premature mainly because of delays in recertification of NBs, and few submissions by manufacturers; and it was difficult for NBs to participate when they were preoccupied with implementing the MDR and coping with the COVID-19 pandemic.
- The anonymised EUSurvey was revised, with 4 general questions, for ***retrospective*** study of the use of conditions on certificates issued under the EU Medical Device Directives. 40 NBs were invited to participate, by individual letters and by presentation to a meeting of the EU Notified Bodies Coordination Group (NBCG-Med).
- A systematic review was performed according to a pre-established protocol.

Findings

- 13 NBs responded, with data based on issuing 2,602 certificates for implantable and Class III medical devices. Reasons given for not participating included being asked to complete too many surveys (requested by regulatory authorities).
- Only 3/13 NBs had issued certificates with restrictions or limitations, in 1% to 2.5% of cases.
- Some jurisdictions outside the EU have established conditional approval schemes.

Conclusion and recommendation

- ❖ The absence of the EUDAMED database, the use of non-uniform information systems, and little tradition for undertaking research, made it challenging for notified bodies to provide accurate information about their decisions. Nonetheless it is clear that the option for issuing certificates with conditions has been scarcely used.
- ❖ There is an urgent need for the EU to develop and implement systems for conditional approval of selected high-risk medical devices, in order to ensure the availability of orphan devices and of innovative devices for unmet needs, whilst enabling the development of further evidence.

Jesús Aranda López et al. Post-approval evidence development schemes established by regulatory authorities for high-risk medical devices. A protocol for a systematic review. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023431233

Training, education, and capacity building – A Roadmap with educational objectives for stakeholders

Austrian Institute for Health Technology Assessment, BioMed Alliance, and TEAM-NB

Objectives

To document needs for advanced training in methodological expertise related to the assessment of high-risk medical devices; to develop appropriate educational objectives; and to provide respective recommendations.

Description

- We mapped advanced training facilities in Europe in regulatory affairs and science.
- After exploratory consultations, we conducted an EUSurvey on training needs among Notified Bodies (contacted via the Notified Bodies Coordination Group, NBCG-Med), EU regulators (via the Clinical Investigation and Evaluation Working Group, CIE, of the European Commission), and clinicians (via the Expert Panels managed by the European Medicines Agency; and the member associations of the Biomedical Alliance in Europe).

Findings

- 409 respondents selected the top 3 skills in which they would like further training. Opportunities varied greatly across groups, but educational priorities were similar:

Principal educational needs / skills

Notified body reviewers (n = 37)
- assessment of benefit-risk ratio and thresholds for acceptability
- design and development of medical devices
- methods for evaluating specific high-risk medical devices

Regulators (n = 58)
- assessment of benefit-risk ratio and thresholds for acceptability
- pre-clinical testing (methodology and evaluation)
- design and development of medical devices

Clinicians (n = 278)
- study-designs and their advantages/disadvantages
- assessment of benefit-risk ratio and thresholds for acceptability
- choice of comparators (standard of care vs. sham vs. placebo)

- 12% of clinicians had a "very good understanding" of the regulatory system; a majority thought training would help them to verify if the devices that they use are safe.

CORE–MD recommends multiple and adaptable opportunities for advanced training:

1. A needs-based (modular) curriculum, integrating and extending existing programmes.
2. Training-on-the-job internships ("job shadowing").
3. Expanded roles for the EU Network Training Centre at the European Medicines Agency.
4. Education for clinicians targeted to the regulatory science skills needed in their daily work.

Wild C & Ettinger S. Perceived training needs of regulators, notified bodies and clinicians for a (successful) implementation of the Medical Device Regulation: survey results. Medical Device Regulation. 2023; 20(2): 45–56. **https://globalregulatorypress.com/topic/mdr-ivdr/**

CORE–MD Workshops 2023

CORE–MD held two workshops in November 2023, to consider proposals that are being prepared for publication as final joint recommendations from the whole consortium.

A charter for ethical innovation of high-risk medical devices

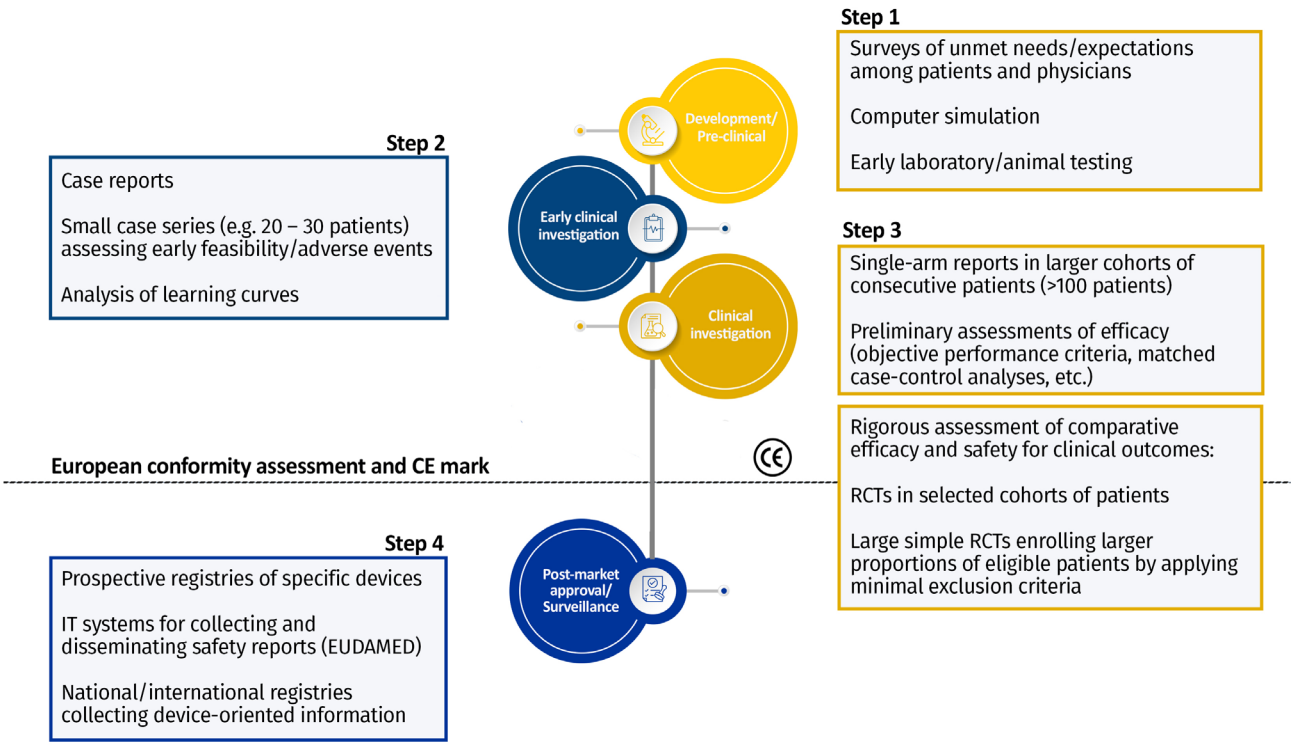
Review of established codes of ethical practice, and guidance from medical professional associations and manufacturers' trade associations, revealed that 9 out of 20 documents explicitly mention medical device innovation. There is a gap relating to specific questions about how to manage competing clinical, academic and commercial interests, while obtaining informed consent, sharing information about unknown risks, and safely managing the staged introduction, dissemination, and monitoring of new technologies – and balancing medical ethics with new EU legislation on data protection that impacts on clinical research.

The CORE-MD charter will create recommendations for all stakeholders involved in the development and approval of new high-risk medical devices:

Developers and innovators / Investigators and trialists / Manufacturers including SMEs and start-ups / Ethics Committees / Notified bodies and regulatory authorities / Reviewers, editors, publishers / Health technology assessment agencies / Physicians and healthcare professionals / and Patients

Recommended methodologies for the clinical evaluation of high-risk medical devices

The research call answered by the CORE–MD consortium asked for advice on a hierarchy of approaches, identification of gaps to be filled by new guidance (e.g. on artificial intelligence), and recommendations on methodologies to obtain sufficient evidence for clinical investigations. This figure shows our initial proposals, that will vary by type of device:



CORE–MD consortium partners

European medical professional associations

- European Society of Cardiology **[Coordinator]**
- The European Federation of National Associations of Orthopaedics and Traumatology
- Biomedical Alliance in Europe
- European Academy of Paediatrics

European umbrella organisation for patients' groups

- European Patients' Forum

Academic institutions

- Leiden University Medical Center
- The University of Oxford
- Uppsala Clinical Research Center
- Royal College of Surgeons of Ireland
- Insel Gruppe AG - Bern University Hospital
- Katholieke Universiteit Leuven
- UMIT Tirol – University for Health Sciences and Technology
- University of Gothenburg
- Politecnico di Milano

National regulatory authorities of EU Member States

- Health Products Regulatory Authority
- Danish Medicines Agency
- Office for Registration of Medicinal Products, Medical Devices and Biocidal Products in Poland

National Public Health Institutes

- Dutch Institute for Public Health and the Environment
- Istituto Superiore di Sanità

Health technology assessment bodies

- Austrian Institute for Health Technology Assessment
- Fundación Pública Andaluza Progreso y Salud – Andalusian Health Technology Assessment Unit

Trade association for European Notified Bodies

- The European Association for Medical Devices of Notified Bodies

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CORE-MD Webinars on the regulation of high-risk medical devices

1. Orthopaedic implants and European Medical Device Regulations
2. The origins of European regulations
3. Objective performance criteria
4. Training and education for regulators, notified bodies and clinicians
5. Recommendations for the clinical evaluation of AI medical devices
6. Evidence for high-risk cardiovascular devices
7. Pivotal clinical investigations of high-risk medical devices
8. IT tools for regulatory science (the CORE-MD search engine)
9. Providing high-risk medical devices for children – problems and proposals
10. Early clinical investigations of new high-risk medical devices
11. Monitoring the life cycle of an implant in real life
12. Patient reported outcome measures
13. The notified body role and the conformity assessment process

Each webinar lasts for 75 minutes, and includes several short presentations and a discussion.

All webinars can be accessed online:
https://www.core-md.eu/core-md-webinars/

CORE–MD deliverables and publications are available at:
https://www.core-md.eu/library

CORE-MD

Coordinating Research and Evidence for Medical Devices

Led by the **European Society of Cardiology (ESC)** in close partnership with the **European Federation of National Associations of Orthopaedics and Traumatology (EFORT)**, the consortium includes **22 partners** involved in the development, evaluation, approval and certification, clinical use, and monitoring of medical devices.

Discover the project

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