CORE-MD

Coordinating Research and Evidence for Medical Devices

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(Coordinating Research and Evidence for Medical Devices)

WP1 - T1.1

Clinical evidence for high-risk medical devices in cardiology: a protocol for a systematic review and meta-epidemiological investigation.

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Duration: M1-24

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 965246

ABSTRACT

Introduction: Experts should advise on the evaluation process of high-risk medical devices in clinical investigations to derive information that informs regulators to make appropriate judgement and decisions in terms of innovation, safety, performance and cost-effectiveness. Implementation of the new Medical Device Regulation (European Union) challenges the medical community to engage with regulators, notified bodies and industry to develop transparent, rigorous and proportionate methods to evaluate the clinical safety and efficacy of devices and monitor their performance. Against this background, as part of the EU CORE-MD project, we aim to perform a systematic review to critically evaluate the methodologies applied in clinical investigations to evaluate high-risk medical devices in cardiovascular medicine.

Methods and analysis: We will search Ovid MEDLINE, Embase, and Cochrane CENTRAL, for studies of prospective design evaluating prespecified high-risk medical devices in the field of cardiovascular medicine. The protocol of the systematic review has been prepared according to the statements of preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P). Search strategies and inclusion criteria will be adapted to retrieve relevant clinical evidence of interest for devices in the fields of cardiovascular medicine in different

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databases. Pre-specified information on design, patient population, indexed intervention, and primary outcome(s) will be abstracted on study level. We will identify problems and rank study designs based on their quality and appropriateness. We will also consider age-/sex-specific analyses, and identify reporting on sex-dimension usage in the reviewed study designs and statistical methods. Qualitative data analysis and descriptive statistics will be used for abstracted variables. We will assess differences in characteristics of study design and patient populations relative to CE-Mark approval (studies performed before versus studies performed after CE-approval) within the same class of device but also across different classes of high-risk cardiovascular medical devices.

Ethics and dissemination: Due to the nature of the review and the publicly available material, no ethics committee approval is required. The results will be disseminated through peer-reviewed publications and submitted for conference presentation.

Keywords: high-risk medical devices; class III medical devices; implantable devices; cardiovascular prostheses.

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INTRODUCTION

Rationale

Independent researchers have difficulties to undertake detailed analyses of the clinical evidence that has been submitted to Notified Bodies in the European Union in support of applications for approval of new high-risk medical devices, because the Medical Device Directive 93/42/EEC applies a presumption of confidentiality to the clinical evaluation for a medical device. [Article 20 of the Directive] Until the Medical Device Regulation (MDR) will provide greater transparency for clinical trials of medical devices in Europe, [1] certain insights can be derived from studies of medical devices submitted for regulatory approval in the USA. There, during the period 2000 to 2007 only 31% of 78 premarket approvals were supported by evidence from more than one randomized controlled trial. [2] New devices have often been approved based on evidence that has not yet been published, and iterative changes to their design or manufacturing process have often been accepted without the submission of new clinical evidence. [3] In the USA most orthopaedic devices have been approved not by pre-market authorization but by the 510(k) pathway (using evidence from equivalent, so-called "predicate", devices) with limited clinical trials data, although this has been associated with a 12-times greater

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risk of recall. [4] Complications have also been reported with devices approved for use in patients with diabetes mellitus. [5,6]

With few exceptions, a new drug is likely to be approved only with evidence of safety and efficacy from large scale randomized controlled trials. To evaluate the safety and performance including the clinical benefit of medical devices, sham-controlled randomized trials of devices are possible [7] but most device trials are unblinded or lack adequate control groups. In the past, when high-risk devices were approved in the EU on the basis of limited data related to proof of mechanism of action, it was argued that post-market surveillance would reveal unforeseen issue. [8] The MDR has introduced restrictions with respect to the use of data from equivalent devices for the purpose of market entry, with a contract required between the respective manufacturers for high-risk devices. [MDR, Article 61(5)]. Following CE mark approval, post-market surveillance and clinical follow-up studies are mandatory. Manufacturers will be able to submit clinical evidence collected independently by academic bodies or medical associations, but standards are required to ensure the quality and reliability of such data and to establish methods for sharing data. There are also concerns that the administration of clinical trials has become too complex and cumbersome [9] and that costs have risen disproportionately. Setting appropriate balance between regulation and innovation, pre- and post-market clinical studies, and complex or simpler criteria for approval,

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has to be done following basic principles and considering the best interests of patients.

Along these lines, concerns have been expressed by some developers of medical devices that the new EU regulatory requirements may prevent innovation and delay market access. While the EU has introduced its new legislation, the US Food and Drug Administration (FDA) has advanced the scheme of Innovation Pathway for the accelerated assessment of new devices that has increased the number of first-in-man studies being conducted in the USA. [10] Approval delays may disadvantage patients in the EU from timely access to innovative new devices although it was previously reported that high-risk medical devices that had been approved first in the EU rather than in the USA were associated with a higher rate of recalls. Conversely, there are reports suggesting, [11] that high-risk medical devices approved by the FDA early feasibility program have higher recall rates and shorter times on the market before serious recalls, than devices approved by the previous standard processes. [12]

Objectives

Against this background, an overview of clinical trial designs and methodologies of high-risk medical devices approved in the EU is needed to understand current practice and provide a platform to consider new recommendations. As part of the

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Coordinating Research and Evidence for Medical Devices (CORE–MD) consortium [13], we aim to perform a systematic review of the methodologies applied in clinical investigations that have been used to evaluate high-risk medical devices broadly used in the fields of cardiovascular medicine, identifying problems and ranking study designs for their quality and appropriateness. We will also consider systematic sex-specific analyses, reporting on sex-dimension usage in the reviewed study designs and statistical methods.

METHODS

The study protocol has been developed based on previously established guidelines for reporting and conducting qualitative research by using rigorous and systematic approaches (Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) [14]. The final version of the systematic review will be prepared based on the updated PRISMA 2020 statement [15]. Items of both guidelines' statements have been considered as applicable.

Protocol and registration

The protocol is registered in PROSPERO and published on the website of CORE-MD consortium (www.core-md.eu).

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High-risk medical devices of interest

We will review the clinical evidence of Class III, long-term implantable devices in the field of cardiovascular medicine. A summary of the prespecified devices of interest is provided in Box 1. The following classes of high-risk medical devices in the cardiovascular field will be evaluated: bioresorbable scaffolds (BVS) for percutaneous treatment of coronary artery disease; left atrial appendage occlusion (LAAOC) devices for thromboembolic stroke prevention; transcatheter aortic valve implantation (TAVI) for treatment of severe symptomatic stenosis of native aortic valves; transcatheter mitral valve repair/replacement (TMVR) for treatment of native mitral valve disease; surgical heart valve replacement for native aortic and mitral valve pathologies; leadless pacemakers; and subcutaneous implantable cardioverter-defibrillators (S-ICD). We did not aim to include every available high-risk device in the cardiovascular field, but to evaluate a representative sample of classes of devices used for common medical cardiovascular conditions, which are widely used in the EU. The final list of devices has been defined in consensus with participants of the CORE-MD consortium from different disciplines. We selected the groups of devices based on criteria such as incidence of disease and resulting market volume (in units), the impact of the device on the disease and devices that respond to an unmet need. We will not include coronary drug-eluting stents, since a comprehensive systematic review under the auspices of the ESC was performed in

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2015 [16] in response to a request by the Clinical Investigation and Evaluation (CIE) Working Group of the European Commission with corresponding recommendations for future clinical trial methodology, but will include coronary bioresorbable scaffolds.

Information sources, search strategies, and study eligibility

Search strategies for each device category (class) will be adapted to retrieve publications of interest from different online bibliographic databases. We will search PubMed, EMBASE, and The Cochrane Central Register of Controlled Trials (CENTRAL) with device-sensitive search algorithms (each iteration of a specific device will be considered separately) for peer-reviewed publications of interest. For each specific device iteration, we will focus on the corresponding main product line. The applied search algorithms will be provided along with the final report of our evaluation. For each device of interest, and possible generations thereof, we will retrieve the date of the first CE-Mark approval. The date of CE-Mark approval will be defined through press releases available online, information provided by regulatory sources such as notified bodies, and personal communications with the corresponding manufacturers. The time-span of our interest is 20 years (01.01.2000 to 31.08.2021). The above search strategy will allow us to review a considerable body of the clinical evidence available for each device around the milestone of CE-

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Mark approval and also to summarize evidence relevant to post-market surveillance.

We will focus on any study of prospective design (non-randomized or randomized clinical trials (RCTs) of any design) in humans. We will include reports of studies that clearly define a prospective design or studies clarifying the evaluation of the device by protocol prior to patient recruitment and after ethics committee approval. Studies of any sample size will be considered. Retrospective studies will be excluded. We will exclude RCTs in which the randomization is not on the device-level. Eligible studies should evaluate at least one of the devices of interest in comparison to any control group (active intervention, sham-procedure or no intervention). Different reports of the same prospective study (either non-randomized or randomized) will be identified and will be jointly considered for analysis purposes. For devices related to "structural heart interventions", we will include studies evaluating the device of interest only in native anatomical heart structures (i.e. studies on transcatheter aortic valve implantation (TAVI) for valve-in-valve interventions will be excluded as well as TAVI in mitral or other valve positions). We will not consider case reports, reviews, systematic reviews, meta-analyses, or expert opinion documents. We will not apply any language restrictions. We will initially screen titles and abstracts, obtain full texts of potentially relevant articles and finally determine eligibility. Initial eligibility assessment in title and

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abstract level will be performed by a single reviewer. A second reviewer will check independently the initially identified reports for eligibility. Whenever uncertainty occurred in this step, a third reviewer will be consulted and the final decision made will be based on consensus. Potentially eligible studies will be reviewed in full-text.

Data abstraction and processing

Data abstraction from eligible studies will be performed on study-level for each device of interest in prespecified calibrated forms. The different reports of the same study (i.e. different reports of the same prospective cohort or different reports of the same RCT) will be treated as single unit for data extraction and analysis. For each eligible study, one reviewer will extract the prespecified data of interest. The following PICO (population/study, intervention, comparator, and outcome) elements of interest will be extracted from each study:

- *Population/study:* journal, sample size, number and geographic areas (Europe, North America, South America, Asia-Pacific) of participating sites, year of publication, recruitment period, funding sources (industry-related / non-industry-related / both / none declared), previously registered study-protocol in dedicated platform or protocol previously available in peer-reviewed publication, study design (non-randomized (specify), randomized (superiority, non-inferiority, equivalence)), different time-points of follow-up

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duration, patients lost to follow-up, drop-outs and cross-over patients, whether the authors report any power calculations (if yes, details will be also extracted (power, alpha-level, planned sample size, expected effect size), whether interim analysis was performed (in which framework), whether the final statistical analysis was done in frequentist or Bayesian framework or both, whether the authors cite and suggest a previously published report regarding further details of the study design or the study protocol was available in a clinical trials registry. We also mention whether the study was prematurely terminated and we also record the reasons reported. We will summarize patient and procedural characteristics related to each device. Finally, we will scrutinize the main document and any accompanied supplementary material for information related to patients' involvement in any stage of study design, conduct of the study or results interpretation.

- *Intervention/Comparator:* the index device of interest (specify), comparator devices (specify) and the "control" intervention(s) (if any) will be specified in each study (medical therapy, devices, drug-delivery devices, non-drug treatments including sham interventions or surgery, or no-comparison (single arm studies)). We will not be able to directly address learning curves in the absence of pre-specified protocol specifications or context factors.

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Device modifications resulting in relabeling or indication expansion will be captured along the lifecycle of a given device.

- *Outcome(s):* We will specify the primary outcome or co-primary outcomes of interest in each study. For each primary outcome we will specify whether it is single/composite (the components will be recorded), binary/continuous/discrete (for each outcome), clinical/non-clinical (i.e. laboratory information, imaging)/both, surrogate endpoint(s), risk prediction score(s) (as component of a composite endpoint or single primary endpoint). We will mention whether device-related complications are specifically described. The metric used for the primary outcome, the effect size and the time-point of the assessment during follow-up will be recorded. We will also record whether the investigators provide information related to the primary outcome and sex/age-specific subgroups and whether they claim a subgroup-specific difference for the primary outcome. We will record whether the results are in favor of the index device for the primary outcome, and whether the authors claim sex- or age-specific differences for the primary outcome. Finally, we will mention the method of outcomes adjudication, if reported. Of note, some outcome definitions are subject to change over time and we will use those reported for the primary endpoint

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and at time of longest follow-up. We will also assess time-dependent changes in outcome parameters during long-term follow-up.

Quality assessment of the studies

We are expecting to include heterogeneous studies of different designs. The quality of the included studies will be evaluated by using dedicated tools in a second stage. We will assess the risk of bias in the results of randomized and non-randomized studies that compared the effect of the indexed device compared to other intervention(s) by using the dedicated tools of Risk of Bias (RoB) 2 [17] and Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) [18], respectively.

Data analysis

Reports of different timepoints of follow-up which correspond to the same study population will be considered for the purpose of analyses as a single unit. Using descriptive statistics, we will summarize study characteristics, and interventions of eligible clinical studies for each device and also for each class of device. We will describe and compare differences among different study designs (i.e. prospective cohorts versus randomized trials) for different products in the same class of device but also across different classes of devices. We will summarize and compare characteristics of the clinical studies that were available prior to the approval for market release (CE mark) of the device and the quality of evidence obtained post-

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market approval across major device categories and different devices within each category. We will also look at the cumulative exposure of patients to the device at study level. For each sex- and age-specific treatment subgroup analysis provided, we will record whether a nominally statistically significant ($p< 0.05$) sex/age-treatment interaction was observed for the primary outcome. The studies will be ordered by ascending year and we will evaluate formally statistically significant differences in characteristics in the earlier compared to later studies. The above comparisons between independent groups will be performed with Fisher's exact, Mann-Whitney U, and Kruskal-Wallis tests, as appropriate. Data analyses will be performed using R (R Core Team, www.R-project.org/). All p values will be two tailed with conventional nominal statistical significance claimed for $p<0.05$.

Patient involvement

No information on individual patients will be considered in the current analysis. However, patients will be asked to advise on the interpretation of the findings and the written summary of the results, and may be involved to design future studies or help in the implementation of the study findings.

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Funding and data sharing process

The project is supported by a grant from the European Union (CORE MD, Grant Agreement 965246). The abstracted information of the selected studies will become publicly available.

DISCUSSION

Experts should advise how high-risk medical devices ought to be investigated so that regulators can arrive at appropriate judgement and objective evaluation of the innovation, safety, performance and cost-effectiveness of the medical devices. Implementation of the new Medical Device Regulation (EU) 2017/745 challenges the medical community to engage with regulators, notified bodies and industry to develop transparent, rigorous and proportionate methods for evaluating the clinical aspects of devices and monitoring their safety and performance. The CORE–MD consortium will address this challenge in a unique collaboration between medical associations, EU regulators, national public health institutes, notified bodies, academic institutions, patients' groups, and health technology assessment agencies, with participation of manufacturers' trade associations.

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The consortium is led by two major European Medical Associations – the European Society of Cardiology (ESC) and the European Federation of National Associations of Orthopaedics and Traumatology (EFORT) – with 34 other European medical specialist professional Associations through their joint membership of the Biomedical Alliance in Europe. Ultimate goal of the CORE–MD consortium will be to exploit this network to share experience and to develop expertise within the clinical community in Europe to investigate and assess high-risk medical devices. The consortium will build on existing European and global initiatives and its reports will be opened to public consultation. Final recommendations from the CORE–MD consortium will be presented at the Working Group on Clinical Investigation and Evaluation of the European Commission, so that they can be considered as the basis for developing EU guidance documents or common specifications.

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BOX. List of high-risk cardiovascular medical devices.

Class of device	Devices
Coronary bioresorbable scaffolds	**- Absorb GT1** Bioresorbable Vascular Scaffold System [Abbott] - **Arterial Remodeling Technologies (ART-Stent)** [Arterial Remodeling Technologies S.A.] - **DESolve** and **DESolve 100** (DESolve Scaffold System) [Elixir Medical] **- Magmaris** Coronary Resorbable Magnesium Scaffold [Biotronik] - **Meres** (MeRes100 Bioresorbable Scaffold) [Meril Life Sciences]
Percutaneous devices for left atrial appendage occlusion	**- Amplatzer Cardiac Plug, Amplatzer Amulet** [Abbott] - **Watchman, Watchman FLX** (1st and 2nd generation) [Boston Scientific] - **LARIAT** Suture Delivery Device [SentreHEART] - **LAMBRE** [Lifetech Scientific] - **Cardia Ultraseal** [Cardia]
Transcatheter aortic valve implantation systems	**- Centera** [Edwards] **- CoreValve, CoreValve Evolut R, CoreValve Evolut Pro, CoreValve Evolut Pro+** [Medtronic] **- Direct Flow** [Medical] **- Engager** [Medtronic] **- Jena Valve** [JenaValve] **- J-Valve** [JC Medical] **- Lotus, Lotus Edge** [Boston Scientific] **- Myval** [Myval] **- NVT Allegra** [Biosensors] **- Portico** [Abbott] **- Sapien, Sapien XT, Sapien S3, Sapien 3 Ultra** [Edwards Lifesciences] **- Symetis Acurate TA, Symetis Acurate Neo, Symetis Acurate Neo 2** [Boston Scientific]

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Transcatheter mitral valve repair/replacement systems	**<u>Edge-to-Edge Repair:</u>** **- MitraClip, MitraClip NT, MitraClip NTR, MitraClip XTR, MitraClip G4** [Abbott] **- PASCAL, PASCAL Ace** [Edwards Lifesciences] **<u>Annuloplasty:</u>** **- Cardioband** Mitral Reconstruction System [Valtech Cardio / Edwards Lifesciences] **- Carillon Mitral Countour System** [Cardiac dimensions] **- Mitralign** [Mitralign Inc / Edwards Lifesciences] **<u>Mitral Valve Replacement:</u>** **- Tendyne** [Abbott] **<u>Other approaches:</u>** **- Harpoon TDS-5** [Edwards Lifesciences] **- NeoChord DS1000** [NeoChord, Inc.]
Surgical valves	**<u>Aortic bioprosthetic:</u>** **- Avalus** [Medtronic] **- Biocor Aortic** [Abbott] **- Crown PRT** [Sorin/Livanova/Corcym] **- Epic Aortic** [Abbott] **- Inspiris Resilia** [Edwards Lifesciences] **- Intuity** [Edwards Lifesciences] **- Intuity Elite** [Edwards Lifesciences] **- Mitroflow** [Sorin/Livanova/Corcym] **- Perceval** [Sorin/Livanova/Corcym] **- Perceval Plus** [Sorin/Livanova/Corcym] **- Perimount Magna, model 3000/3000TFX** [Edwards Lifesciences] **- Perimount Magna Ease, model 3300 TFX** [Edwards Lifesciences] **- Solo Smart** [Sorin/Livanova/Corcym] **- Trifecta** [Abbott] **- 3F Enable** [Medtronic] **<u>Aortic mechanical:</u>** **- Aortic ON-X with Conform-X sewing ring** [Cryolife]

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	- Aortic ON-X with anatomic sewing ring [Cryolife] **<u>Mitral bioprosthetic:</u>** **- Biocor Mitral** [Abbott] **- Epic Mitral** [Abbott] **- Magna Mitral Ease, model 7300 and 7300TFX** [Edwards Lifesciences] **- Perimount Plus, model 6900 PTFX** [Edwards Lifesciences]
Leadless pacemaker	**Micra VR & AV TPS** [Medtronic]
Subcutaneous implantable cardioverter defibrillator	**EMBLEM MRI S-ICD** [Boston Scientific]

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