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

## Citation

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## Review question

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 Coordinating Research and Evidence for Medical Devices (CORE–MD) consortium, 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.

## Searches

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

## Types of study to be included

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. 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. We will not apply any language restrictions.

## Condition or domain being studied

We will consider any medical condition which is related to the interventions of the cardiovascular medical devices of interest.

## Participants/population

We will focus on study populations of diverse medical conditions related to the interventions of interest.

## Intervention(s), exposure(s)

We will review the clinical evidence of Class III, long-term implantable devices in the field of cardiovascular medicine (bioresorbable scaffolds for percutaneous treatment of coronary artery disease; left atrial appendage occlusion devices for thromboembolic stroke prevention; transcatheter aortic valve implantation for treatment of severe symptomatic stenosis of native aortic valves; transcatheter mitral valve repair/replacement 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). 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. 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 2015 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

## Comparator(s)/control

The control interventions can be any of the class of devices of interest (active intervention) or sham-procedure or no intervention.

## Main outcome(s)

For each class of devices/interventions, we will specify the primary outcome or co-primary outcomes of interest in study-level. Primary outcomes in class of devices/conditions we be further classified and jointly considered for analysis.

### Measures of effect

The metric used for the primary outcome, the effect size and the time-point of the assessment during follow-up will be recorded.

## Additional outcome(s)

We will also mention whether device-related complications are specifically described.

## Data extraction (selection and coding)

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 and a second one will be involved to resolve uncertainties. PICO (population/study, intervention, comparator, and outcome) elements of interest will be extracted from each study. Detailed list of extracted information is available in the uploaded protocol.

## Risk of bias (quality) assessment

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 and Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I), respectively.

## Strategy for data synthesis [1 change]

We will use descriptive statistics to qualitatively synthesise the available evidence for each class of device and describe differences between studies before and after CE-Mark of the respective device. Using descriptive statistics, we will summarise study characteristics, and interventions of eligible prospective 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-market approval across major device categories and different devices within each category. The above comparisons between independent groups will be performed with Fisher's exact, Mann-Whitney U, and Kruskal-Wallis tests, as appropriate. We expect considerably different primary outcomes and metrics among the included studies, therefore we are not planning to perform a formal synthesis through meta-analysis.

Data analyses will be performed using R (R Core Team, www.R-project.org/).

## Analysis of subgroups or subsets

For each sex- and age-specific treatment subgroup analysis provided, we will record whether a nominally statistically significant sex/age-treatment interaction was observed for the respective primary outcome(s) and among different classes of devices.

## Contact details for further information

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## Type and method of review

Intervention, Methodology, Synthesis of qualitative studies, Systematic review

## Anticipated or actual start date

13 February 2022

## Anticipated completion date

31 December 2023

## Funding sources/sponsors

The project is supported by a grant from the European Union (CORE MD, Grant Agreement 965246).

## Conflicts of interest

## Language

English

## Country

Ireland, Switzerland, Wales

## Published protocol

https://www.crd.york.ac.uk/PROSPEROFILES/308593_PROTOCOL_20220203.pdf

## Stage of review

Review Ongoing

## Subject index terms status

Subject indexing assigned by CRD

## Subject index terms

Cardiology; Humans

## Date of registration in PROSPERO

11 February 2022

## Date of first submission

03 February 2022

## Stage of review at time of this submission

| Stage | Started | Completed |
|---|---|---|
| Preliminary searches | No | No |
| Piloting of the study selection process | Yes | Yes |
| Formal screening of search results against eligibility criteria | No | No |
| Data extraction | No | No |
| Risk of bias (quality) assessment | No | No |
| Data analysis | No | No |

*The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.*

*The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.*

## Versions

11 February 2022