Orthopedic and cardiovascular medical device registries in Europe: a systematic review

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Introduction

A medical device registry is defined as ‘‘An organized system that continuously and consistently collects relevant data in conjunction with routine clinical care, evaluates meaningful outcomes, and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale (e.g. international, national, regional, and health system) with a primary aim to improve the quality of patient care’’[(1)]. Registries are thus essential for capturing outcomes associated with the implementation and use of medical devices in daily clinical practice after Conformitè Europëenne (CE) approval, and, to demonstrate the impact of health care quality on a larger scale than clinical evidence generated as part of CE approval.

However, systematic assessments of clinical evidence on the safety and effectiveness of medical devices after CE approval is currently lacking[(2)]. Nevertheless, the Medical Device Coordination Group (MDCG) states that determinations of the level of clinical evidence is required to assess safety and performances of medical devices[(3)]. Additionally, the MDCG argues that the acceptability of the benefit-risk ratio must be based on clinical data providing sufficient clinical evidence. Hence, outcomes from high quality clinical data collection

systems, such as registries in which benchmarking is performed using real-world evidence and on a continuous basis, are essential.

The importance and advantage of medical device registries for benchmarking high risk medical devices (e.g. cardiovascular stents and hip implants) is that all patients in which a device is implanted in daily clinical practice are included. This means that patients of different races, all ages, and multiple comorbidities are monitored and not only a selected sample like in Randomized Clinical Trials (RCTs)[4, 5]. Hence, registries not only represent real-world evidence of both outcomes and safety risks in an unselected population, but also provide additional evidence not encountered in RCTs due to the limited follow-up or the low frequency of occurrence[6]. To gain understanding of the performance and safety of medical devices after CE approval, RCTs should therefore be supplemented with evidence from registry data that have: 1) high data completeness on both patient inclusion and outcome measurements; 2) longer follow-up periods, and 3) an accurate view of real-life healthcare provided to the population.

Europe has a long tradition of registries with the first European orthopedic registry founded in 1975 (Swedish Knee Arthroplasty Register, Sweden), and the first European cardiovascular registries in 1977 (National Pacemaker Database, England, and United Kingdom Cardiac Surgical Register, England)[7-9]. Ever since, several countries from all over the world have established both orthopedic and cardiovascular medical device registries, aiming to improve health care quality by monitoring and evaluating the patient outcomes following implant surgery[7, 8, 10]. However, registries may not be consistent in terms of: 1) design; 2) organization; 3) methods used for data collection, and 4) collected outcomes (e.g. different definitions of outcomes)[8, 10]. This is important to enable benchmarking medical devices on their performance and to achieve early detection of any safety concerns for specific implants.

The present review updates an earlier review conducted by Niederländer et al, that identified implantable medical device registries almost a decade ago[10]. We want to expand their review, focusing on orthopedic (knee and hip arthroplasties) and cardiovascular (stent and valves) medical device European registries with the aim to provide a more in-depth overview of these registries including both characteristics that determine quality of the data, definitions used, and outcome data for medical devices in those registries. These were chosen to include both frequently used devices and new technologies for which regulatory guidance is needed.

Objectives of the present systematic review:

1. To characterize orthopedic (knee and hip arthroplasties) and cardiovascular (stents and valves) registries in Europe on variables that determine quality of data and thereby generated evidence, including organization of registries, data collection, definitions and methods used, duration of follow-up and level of detail in reporting outcome data.
2. To examine performance of different types of devices in daily practice including relevant groups to enable benchmarking, and safety concerns of these devices. For orthopedic devices, performance in daily practice will focus on the total construct of the device inserted, including i.e. different combinations of cup and stem for hip implants and tibial / femoral components for knee implants, to examine whether performance depends on the component with which it is combined. We will collaborate with another Work Package (WP task 1.1) who is involved in the same European project (CORE-MD) to determine whether clinical evidence from published studies (i.e. RCTs) relates to performances of medical device in daily practice (i.e. registries).

3. To examine safety concerns reported for medical devices in registries, including the methodology of identifying safety concerns. In collaboration with WP task 1.1, we will assess

whether occurrences of these safety concerns is associated with occurrence as part of the clinical evidence.

Methods

This systematic review will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[11], and will be registered in the Center for Open Science. As Niederländer et al aimed to identify all different types of European medical device registries (e.g. breast implant, cochlear implants and arthroplasties) we will update their algorithm, focusing on orthopedic (knee and hip arthroplasties) and cardiac (stents and valves) medical device registries specifically. It is possible that more recently established and currently active, registries are included, as Niederländer conducted their search up to December 2012. For each registry we will collect characteristics and outcomes (see data extraction) both on registry level and medical device level.

Search strategy

The literature search (Appendix 1) will be conducted in PubMed, Embase, Web of Science, Cochrane Central Library, and Emcare including papers from January 1, 2013 until present. To establish whether we missed some potential registries, we will check the websites of the Network of Orthopaedic Registries of Europe (NORE) and the International Society of Arthroplasty Registries (ISAR), in which all existing national/regional or/and institutional arthroplasty registries in Europe are listed (available: https://efortnet.efort.org/nore-map/#/nore/map-all and https://www.isarhome.org/members). Then, the list of references will be imported to EndNote (Endnote version X9, Clarivate Analytics, Philadelphia, United States) to remove duplicate articles, and subsequently it will be exported to Rayyan (web application, Doha, Qatar) for study selection.

Study selection

All papers describing a registry as identified by Niederlander focusing on knee / hip arthroplasties or cardiac stents and valves will be selected. From the literature search, two authors (L.A.H. and T.H.G.) will independently select further eligible papers based on screening the title and abstract. Any discrepancies will be resolved by discussion, or consulting the senior author (P.M.) for a decisive vote. After title and abstract screening, full texts will be assessed for eligibility independently by the same two authors. As before, discrepancies will be resolved by discussion. According to previously described criteria, we will only include articles in which the design process of an orthopedic or cardiovascular European registry is clearly described[12] which will likely contain variables and methods for data collection. The most complete article or combination of articles describing the registry design will be included. We will add information regarding the registries designs (e.g. new variables) obtained from more recently published articles or other sources (e.g. registries websites). We will exclude European countries which were located in two continents (i.e. Russia and Turkey). There will be no restrictions on language of publication. Additionally, the reference lists of all included studies will be checked, by one reviewer (L.A.H.), to identify other potentially eligible articles which were not found by the literature search. Once the registries are identified along with their names, we will locate their websites and last annual report for further data extraction.

Data extraction

Last updated annual registry reports will be used to collect the most recent data.

On the registry level, we will ideally collect the following characteristics and outcomes:

- Type of registry (orthopedic/cardiovascular)
- Name of the registry

- Website of the registry
- The starting year of registry (first patient included)
- Year of first annual report
- Year of last annual report
- Mandatory (yes/no)
- Patient consent
- Access to registry for users/members? (e.g. dashboard, real-time, and secure server)
- Number of participating hospitals (relative to total in region/country?)
- Data completeness on patient level
- Missing data for variables (% missing and how this is handled, separately for patient characteristics and outcomes)
- Quality assurance/quality check of data (e.g. data verification)
- Funding (e.g. government, private, and manufacturers)
- Type of information provided, for whom and at which level (e.g. device, hospital, and surgeon)
- Actionable data (frequency of data feedback on e.g. medical device outliers, frequency of data review on device outcomes)
- Data capture and collection (e.g. electronic, manual, barcodes-industry, and surgeon-reported)
- Data linkages (e.g. with hospital statistics, manufacturer vigilance data, National Competent Authority on medical devices)
- Transparency and governance
- Total duration of follow-up
- Privacy in country (e.g. unique identifier, which identifier, compliance General Data Protection Regulation (GDPR), and opt-in/out)

- Safety: outlier reports, which implants identified using which methodology

On the medical device level, we will ideally collect the following characteristics and outcomes, for each combination of components (for orthopedic devices):

- Strength of clinical evidence available (link with WP task 1.1: RCT/observational)
- Type of medical device (e.g. model, design features, and European Medical Device Nomenclature (EMDN) class). For orthopedic implants at least fixation, insert and mobile/fixed bearing, material. For cardiovascular at least type (bare metal / drug eluting stents and valves based on location (mitral / aortic / pulmonary / tricuspid-valve) and type (autograft / allograft).
- Total volume in registry
- Annual volume in registry
- Number of hospitals using this device
- Patient characteristics (e.g. % male, mean age, mean BMI, and smoking status)
- Time since market access (link with WP task 1.1)
- Follow-up time of outcome measurements (e.g. 5-year)
- Clinical outcomes (including definitions): % and SE (or calculated from confidence interval) e.g. revision and stent thrombosis
- Patient reported outcomes (including definitions): mean and SD
- Does the outcome relate to safety/harm or benefit
- Registries' definition of outlier devices (e.g. based on 5-year revision rates, ODEP rating for orthopedic devices)

We will contact the registries via email to request additional information not presented in annual reports/papers/registries' website.

Data management

The extracted data will be documented in Excel according to a pre-specified format. Two reviewers (L.A.H. and T.H.G.) will screen all the annual reports, registries' website, and studies and extract all abovementioned characteristics (blinded) in duplicate. Discrepancies will be solved by discussion.

Data analysis

Objective 1 (To characterize definitions and methods used in orthopedic and cardiovascular registries in Europe likely related to quality of generated evidence).

Data will be presented using descriptive statistics, to assess which variables and characteristics are consistently collected across registries. These analyses will be done at the registry level, with some device variables (e.g. annual volume in registry) aggregated at registry level. We will qualitatively assess differences between mature registries that exist for more than a decade, and those established more recently.

Objective 2 and 3 (To examine performance and safety concerns of different types of devices in daily practice based on public available data available from registries' annual reports). Analyses will be conducted separately for orthopedic and cardiovascular devices, as well as for hip/knee arthroplasties and stents/valves.

Orthopedic devices: Devices will be considered as a total construct, meaning that we will consider combinations of components (mix & match) within each type of device. For each combination, a random effects model will be used to pool the all-cause revision percentages and their SE at available follow-up times (e.g. 1, 5 and 10 year) across registries, including a DerSimonian-Lard estimator to estimate heterogeneity. Similarly, we will pool

all-cause revision percentages for a given component (e.g. hip stem) and include the possible cups as a factor to test for a difference between groups, to assess whether the combination determines the revision performance. We will use the I^2 to assess the extent of heterogeneity, using cutoffs of 25% to indicate low heterogeneity, 50% moderate and 75% high heterogeneity. Additionally, similar statistics will be used to analyze PROMs (using mean PROMs scores, including SDs) for each combinations of components. We will perform a post-hoc sensitivity analyses to test the impact of various assumptions on the primary outcome (i.e. revision surgery) and for the influence of type of design on performance.

Cardiovascular, stents: We will analyze bare metal stents (BMSs) and drug eluting stents (DESs) separately. For each type of stent (based on CE marks), a random effects model will be used to pool the mortality as well as stent thrombosis percentages and their SE at available follow-up times (e.g. 1, 5 and 10 year) across registries, including a DerSimonian-Lard estimator to estimate heterogeneity. We will use the I^2 to assess the extent of heterogeneity using cutoffs of 25% to indicate low heterogeneity, 50% moderate and 75% high heterogeneity. In case of considerable heterogeneity, we will explore whether specific brands or types have different performance using similar stratified analysis. We will perform a post-hoc sensitivity analyses to test the impact of various assumptions on the two primary outcomes (i.e. stent thrombosis and mortality).

Cardiovascular, valves: We will analyze mitral-, aortic-, pulmonary-, and tricuspid-valve separately. Additionally, we will further categorize the valves on type of valve: autograft *versus* allograft. For each type of valve, a random effects model will be used to pool the mortality percentages and their SE at available follow-up times (e.g. 1, 5 and 10 year) across registries, including a DerSimonian-Lard estimator to estimate heterogeneity. We will use the I^2 to assess the extent of heterogeneity using cutoffs of 25% to indicate low heterogeneity, 50% moderate and 75% high heterogeneity. In case of considerable

heterogeneity, we will explore whether specific brands or types have different performance using similar stratified analysis. We will perform a post-hoc sensitivity analyses to test the impact of various assumptions on the primary outcome (i.e. mortality).

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