Safety and performance of high-risk medical devices: the role of real-world data

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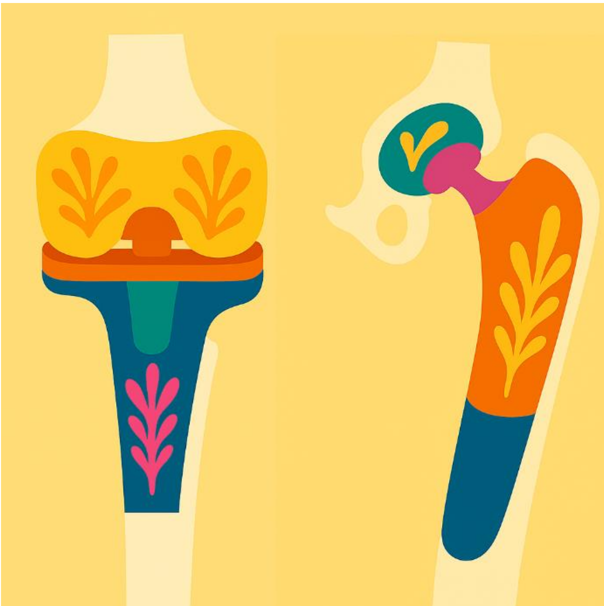
Chapter 1 – General introduction and outline of the thesis



Historical perspective of arthroplasty implants

One of the most frequently used medical devices in orthopedics are traumatology implants (e.g. nails and plates) and arthroplasty implants. The latter referred to as joint replacement implants, joint prosthesis, or artificial joints.[1] The earliest written evidence of the use of a prosthetic implant refers to the "Rig Veda", a sacred Indian poem (3500 – 1800 Before Christ).[2,3] This poem recounts the story of a warrior-queen, who lost her leg while fighting a battle. To enable her to return to the battle, her leg was replaced by an iron prosthetic implant.

Whereas the prosthetic amputee implant used in Rig Veda is written evidence of the use of a prosthesis, the oldest arthroplasty implant found by archaeologists originates to the ancient Egyptians. A female mummy was found at the necropolis of Thebes-West (built 1500 – 1300 Before Christ) with a missing big toe on her right foot.[2] The missing toe was replaced by a wooden prosthesis including a joint (i.e. an external arthroplasty implant) consisting of three separate well-manufactured components; a "body" (replacing the toe) and two smaller wooden plates, used for keeping the "body" in the correct position. This construction was expected to provide sufficient stability and to allow her to move without major restrictions.

Next to these external amputee prosthesis used for amputated limbs, the first "in-body" arthroplasty implant has been described in the 19th century by Professor Themistocles Glück.[4,5] Glück designed and implanted arthroplasty knee and hip implants made from ivory. Although Glück's arthroplasty implants were deemed successful in the short term (i.e. the first two years), longer follow-up results were less favourable, with all implants ultimately failing due to chronic infection.[4] Around the same time, the first total shoulder arthroplasty implant was implanted in 1893 by the French surgeon Péan.[6]

Innovations in both arthroplasty materials, designs and surgical techniques have greatly improved since the 19th and early 20th century with the development of better implant materials. Also, since the 1970s -1980s with better, more reproducible surgical tools. Since the 1990s, total hip and total knee arthroplasty implants are considered the most successful treatments for several hip- and knee-related disorders and diseases, while also one of the most commonly performed elective surgeries worldwide.[7-9] Unfortunately, despite these improvements in both implants and surgical technique, failures related to the safety and performance of arthroplasty implants still occur.[10-12] The latter and the fact that the number of arthroplasty surgeries performed worldwide is still increasing , demands for a more rigorous system for evaluating clinical evidence of arthroplasty implants.

The most commonly used clinical outcome to indicate the safety and performance of orthopedic arthroplasty implants is “revision surgery”. Revision surgery can be done with or without component exchange.[13] Revision without the exchange of components is usually performed in case of implant loosening. Revision with component exchange (i.e. replacing the old component for a new component) is the most commonly used clinical outcome, since it has significant consequences for the patient (e.g. undergoing a re-operation, having a higher risk of infection when compared to primary arthroplasty, and worse patient reported outcome measurements (PROMs)).[14-17] Next to the impact for patients, revision surgery also leads to incurring personal and societal costs.[18]

A well-known safety incident in the field of arthroplasty implants relates to the metal-on-metal total hip arthroplasty implants.[12,19,20] Originally developed as a more durable alternative to total hip arthroplasty implants that incorporated ceramic or polyethylene components, mid-term follow-up registry data of patients with metal-on-metal total hip arthroplasty implants showed far higher revision rates when compared with other total hip arthroplasty implants.[12] In addition, literature showed the occurrence of pseudo-tumours and adverse reactions to metal debris in patients with metal-on-metal total hip arthroplasty implants.[12,20] As a consequence, metal-on-metal total hip arthroplasty implants were taken off the market (“recalled”) by their manufacturers to prevent further patient harm. However, at the time of recall, many metal-on-metal total hip arthroplasty implants were already implanted in patients, affecting over one million patients worldwide.[12,21] The case of metal-on-metal total hip arthroplasty implants demonstrates that to prevent patient harm it is important to use orthopedic medical devices with high safety and good performance[22] as well as the need for monitoring the performance of devices after they have entered the market, to detect any devices with safety concerns as soon as possible.[23,24]

Bringing a medical device on the European market

The regulation regarding medical devices as set by the European Union defines requirements of medical device design and fabrication to ensure quality assurance and safe use of medical devices.[25] The first European directive on medical devices (MDD) came into force in 1990.[25-28] Since then, several amendments to this directive have been made, resulting in stricter and more explicit requirements on the safety and performance of medical devices. In 2017, the European Union has significantly revised its regulatory framework by the Medical Device Regulation.[29] The Medical Device Regulation has a four-year transition period, which was extended to 2028. The aim of the new regulatory framework is to provide clinical evidence and to improve patient safety while ensuring that innovative medical devices remain available for patients.[30]

Before new medical devices can be introduced to the European market, they must first obtain a "conformité européenne" (CE) marking.[31] The CE marking for medical devices implies (but does not guarantee) that the medical device meets the general safety and performance requirements.[31] These general safety and performance requirements are set by European authorities to ensure that new medical devices will be safe and perform as intended throughout their entire life cycle. Once a medical device has attained a CE marking, it is approved to be sold in the European member states and thus allowed to be used in patients. To obtain a CE marking, clinical evidence has to be collected and reviewed by manufacturers (i.e. pre-market clinical investigation) to show that their medical device is safe, has good clinical performance and an acceptable benefit/risk ratio.[24,31,32]

The pre-market clinical investigation must be objective, which means that both favourable (e.g. high implant survival percentages, low number of adverse events, and good PROMs) and unfavourable (e.g. low implant survival percentages, high number of adverse events, and low PROMs) clinical data have to be included. If the conformity of the medical devices are deemed to be sufficient, the device will be certified with a CE marking. However, CE marking does not indicate that a medical device is effective, only that it complies with the legal requirements.[31] Moreover, pre-market clinical evaluation is an assessment of clinical data from any relevant source, including literature on similar medical devices.[31] Thus, the pre-market clinical evaluation may not include an extensive analysis of real-world data of the actual medical device used in all patients. In addition, pre-market clinical investigation is often based on studies with a relatively short study duration when compared with their (expected) long duration of use in patients, thereby not capturing failures at longer follow-up.[31,33,34] Therefore, infrequent adverse events may not be captured due to the relatively short follow-up period or because of a small patient population (e.g. not all patients receiving the medical device might be analysed during pre-market clinical evaluation).[33,34] Given these pre-market clinical investigation shortcomings, manufactures have to show high safety and good performance of their medical device in daily clinical practice after having entered the market to ensure patients' safety, using real-world data.

Real-world data sources to assess the safety and performance of medical devices

For decades, data from randomised controlled trials were considered as the highest-quality evidence in clinical research as they provide the ideal study design to minimise confounding and thereby can demonstrate causality between specific interventions and outcomes.[34-39] However, randomised controlled trials do have limitations such as: i) mostly including highly selective patient populations, often not representative of the general patient population; ii) having a limited period of follow-up and thereby a small chance to capture infrequent adverse events or events that occur at late follow-up; iii) it may pose ethical challenges, and iv) not always the most suitable study design (e.g. when comparing the safety and performance of a specific arthroplasty implant between different countries).[37,38] Consequently, the safety and performance as demonstrated in randomised controlled trials will frequently differ from the safety and performance of medical devices in daily clinical practice.[38,40-42] Hence, outcomes from high quality clinical data collection systems, such as registries where real-world data is collected, are needed.

Different real-world data sources can be used for the detection of any safety and performance concerns for specific medical devices (e.g. electronic health records, administrative data, patient generated data, safety notices, and registries), all having their own strengths and weaknesses.

Data obtained from electronic health records (i.e. an electronic system maintained by healthcare providers to collect and store patients' medical information[43]) may enable clinicians and researchers, after informed consent has been obtained by patients, to exchange information between different hospitals in order to improve the ability to conduct research and (in)directly patient care.[44] On the other hand, the data may be of poor data quality such as incomplete or missing records because they are gathered as part of routine patient care.[45] Administrative data are relatively easily accessible and cost-efficient as well as covering a large patient population. Administrative data however is collected as part of routine care and thus not intended to be used for research purposes, which may lower the validity and reliability of administrative databases for clinical research.[46,47] Patient generated data (i.e. data generated by and from patients) may capture other outcomes, such as PROMs, when compared to the other four data sources. But it may be challenging to get sufficient response rates which limits the generalisability of patient generated data.[48] Another data source which can be used to assess the safety and performance of medical devices are safety notices. Safety notices can be viewed as incident reporting data, issued when an adverse event related to their medical devices triggers action from the manufacturer.[49] Incident reporting is often voluntary, where known disadvantages include that it is heavily influenced by reporting behaviour and therefore primarily reflects the safety culture of e.g. an organisation rather than the underlying safety epidemiology.[50] However, safety notices are legally mandatory to be reported and therefore less influenced by reporting behaviour. They are typically publicly reported on the websites of national competent authorities or regulatory agencies. Safety notices can be issued for a wide variety of issues (e.g. from packaging and labelling to material integrity). Thus, these safety notices do not always indicate a problem with the mechanical or clinical performance of a particular medical device. Although reporting safety notices is legally mandatory, safety notices only provide the numerator of a possible safety concern "the number of devices with safety concerns" and not the denominator "how many patients are at risk to develop a safety concern" (i.e. in which the devices were implanted). Medical device registries have both the numerator as well as the denominator, if high implant-level completeness is present, which makes them well suited to provide clinical evidence of the safety and performance of medical devices used on the market.

A registry is defined by the International Medical Device Regulators Forum as an "organized system with a primary aim to increase the knowledge on medical devices contributing to improve the quality of patient care that continuously collects relevant data, 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)".[51] A medical device registry is thus an unselected population-based health information system collecting large numbers of real-world data regarding the safety and performance of specific medical devices over time, while having a longer follow-up period than in randomised controlled trials. The main purpose of arthroplasty registries is to collect information on all patients receiving a specific arthroplasty implant to monitor and improve clinical outcomes.[52] The value of registry data is internationally acknowledged, which has resulted in a strong rise of hospital-based, regional, and national arthroplasty registries in the last century (Figure 1).

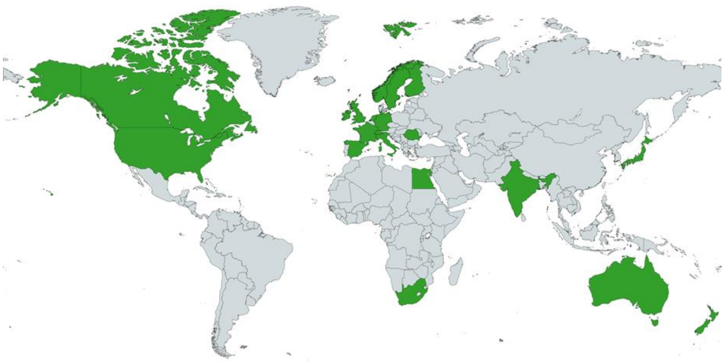


Figure 1. *World map of countries (coloured in green, n=29) with a hospital-based, regional or national arthroplasty registry (Figure adapted from the International Society of Arthroplasty Registries template "Arthroplasty registries at a glance"[53])*

Registries may however vary in terms of: i) design; ii) organisation; iii) methods used for data collection, and iv) collected outcomes (e.g. different definitions of outcomes and follow-up durations).[54,55] Such variation in structural and methodological characteristics may influence the quality of data collected. In addition, individual registries may not have sufficient sample size to analyse the safety and performance for less frequently used medical devices, requiring coordination and collaboration of registries across countries. Pooling data across registries has several benefits, such as: i) a larger set of data, which will better reflect daily clinical practice while also allowing to analyse less frequently occurring adverse events, and ii) potentially resulting in earlier detection of safety and performance issues for specific medical devices. Before pooling data across registries could be achieved, consensus on a common dataset of outcomes (including similar definitions) that all medical device registries would collect is needed. Several principles have been proposed by orthopedic associations (e.g. the Network of Orthopaedic Registries of Europe (NORE)[56]) and regulators (e.g. the International Medical Device Regulators Forum (IMDRF)[57]) to evaluate whether the quality of data used to assess the safety and performance of medical devices on the market meets the scientific standards including; coverage ("the extent of participation in data collection"), completeness ("data used in analyses are consistently captured"), accuracy ("data recorded is an accurate reflection of the healthcare event"), consistency ("uniformity in following the same procedures for data capture"), integrity ("consistent recording of unique identification of medical devices"), and reliability ("reproducibility of data elements")[51]. Specific criteria have however not been proposed, and it is therefore unknown if existing medical device registries meet the medical device regulation requirements to an acceptable standard and can be reliably used to assess the safety and performance of medical devices on the market.

Methods used to evaluate the safety and performance of medical devices

In orthopedic practice, different methods to assess the safety and performance of arthroplasty implants are currently used to guarantee that clinicians and hospitals select the best-performing implants, in which implants are compared to: i) the best-performing implant, based on implant survival analysis (i.e. revision as end-point); ii) the average performance (again, based on implant survival analysis) of other comparable implants, and iii) absolute thresholds by using objective-performance-criteria.[58-68] Arthroplasty registries have different approaches in place for identification of outlier implants (i.e. implants having a significantly worse performance (i.e. revision) than expected), mainly using the first two methods; comparing specific implants to the best-performing implants or to other comparable implants. Outlier identification in registries has resulted in multiple outlier medical devices being taken off the market.[58]

Using an absolute threshold (i.e. objective-performance criteria) has the benefit of relatively easy interpretation and thereby making the assessment of implant safety and performance more straightforward. The limitation of absolute thresholds is that they may have to be updated over time (given that implants performances may change over time), so it has to be considered whether the absolute threshold is still acceptable. The most frequently used objective-performance-criterium in orthopedic practice is the Orthopaedic Data Evaluation

Panel (ODEP) rating.[62] The ODEP criterium is designed and used to promote evidence-based selection of orthopedic implants by assigning a rating (the ODEP-rating) to orthopedic implants based on implant survival analysis criteria (i.e. revision rates). ODEP ratings are available for TH components (cups and stems), TK implants (tibiofemoral combinations), unicondylar knee implants, shoulder components (glenoids and stems), reverse shoulder implants, total elbow implants, and spine implants (cervical discs). As different data sources can be used by manufacturers to submit their application for an ODEP-rating (e.g. single-center studies, manufacturers' in-house sources, and registry data), this data may not be representative of daily clinical practice. Therefore, before submission, manufacturers must declare that "the clinical data submitted is representative of all studies that have been conducted in relation to it." Although originally focused on the United Kingdom, the ODEP-rating is increasingly used in other countries for the quality assessment of arthroplasty implants.[69-71] Despite being increasingly used, external validation of ODEP-ratings across multiple registries has never been undertaken. Therefore, it is unclear whether the performance of a particular implant in another country than the United Kingdom is consistent with the assigned ODEP-rating and thereby if surgeons or hospitals outside the United Kingdom can use the ODEP-rating to guide implant selection.

The safety and performance of a specific medical device may however differ between hospitals within a single registry, but also between registries, as research has shown that besides factors related to the medical device itself, there are many more factors influencing the safety and performance of medical devices.[72-74] Focusing on arthroplasty implants, patient related factors (e.g. body mass index (BMI), comorbidity classification, gender, and indication for surgery) may differ between specific implants and are known to influence revision rates and clinical outcomes.[72,73,75-77] Thus, before differences in revision risks between registries for specific implants can be interpretated, a better understanding of any differences in patient characteristics between registries for specific implants is needed, which may also point to differences in patient selection for the same implant across registries. Only a few studies have assessed differences in patient characteristics across registries.[78,81] However, the majority of these studies only focused on variations in pre-operative pain and function levels, even more important, all these studies analysed all arthroplasty implants combined (e.g. all cemented total hip implants combined) instead of analysing differences for specific medical devices from specific manufacturers. Hence, a more comprehensive analysis of the similarities and differences in patients receiving these specific arthroplasty implants in different countries is required to better understand differences in implants' safety and performances across registries.

Besides these medical device- and patient-related factors, surgeon- and hospital-factors are known to effect performance of medical devices.[74,82-86] Therefore, an essential part of clinical practice should involve reducing complication risks (e.g. revisions) by continuously improving the quality of care delivered by surgeons and hospitals thereby minimising patient harm and unnecessary costs. Hence, an increased number of arthroplasty registries are providing feedback to orthopedic surgeons and hospitals, with the aim to minimise patients' morbidity and costs.[87-90] This feedback is intended to serve two goals: i) individual hospitals can monitor their performance over time to examine if outcomes are improving or deteriorating, and ii) hospitals performing worse than other hospitals while treating comparable patients, might compare their practices to better-performing hospitals to identify possibilities for improvement. Literature has shown that if this feedback is provided in an active approach by also discussing these results with clinicians, outcomes for patients will improve (e.g. revision of implants decreases, less complications, and a reduced length of hospital stay).[91] However, variation in overall revision risks does not give sufficient information to guide where to improve care as revisions may be performed for different indications (e.g. infection or surgical technique failure) each aligned with different quality improvement initiatives.

In the Netherlands, large between-hospital variation in one- and three-year revision rates following primary total hip and total knee arthroplasty has been found.[74] For most of the hospitals performing worse than expected, a specific indication for revision could be identified as contributing to the overall worse performance. The latter can guide quality improvement initiatives. However, whether this also applies to other arthroplasty implants, such as shoulder arthroplasty implants, is currently unknown. As shoulder arthroplasty, both primarily and revisions, are less commonly performed than hip- and knee-arthroplasty, between-hospital variation in revision rates following primary shoulder arthroplasty might not be reliable given that large numbers (both for primary and revision surgery) are needed to reliably assess between-hospital performances.

Outline of this thesis

This thesis aims to investigate how real-world data of implantable high-risk medical devices – particularly from arthroplasty registries and safety notices – can be used to i) ensure high-quality data and evidence regarding safety and performance of high-risk medical devices, and ii) develop methods for the evaluation of safety and performance of high-risk medical devices.

In **Chapter 2,** European orthopedic registries (hip and knee arthroplasty implants) and cardiovascular registries (coronary stents and valve repair/replacement) will be identified and reviewed on the extent to which 33 structural and methodological items are publicly reported that influence the quality of registry data, as well as the definitions used and reported outcomes. By assessing this, the utility of current orthopedic and cardiovascular medical device registries for regulatory purposes will be examined. Based on these results, a three-round Delphi study will then be conducted, including all stakeholders in the regulatory evaluation of medical devices. This Delphi study aims to achieve consensus on a minimum dataset needed to assess the quality of registry data and analysis of medical device safety and performance (**Chapter 3**).

Combining registry data with other real-world data sources may highlight safety problems that otherwise would remain unnoticed, and therefore **Chapter 4** will assess the extent to which safety notices issued by manufacturers signal the same total knee arthroplasty implants as those identified by registries as outlier implants (i.e. implants having a significantly worse performance (i.e. revision) than expected).

Chapter 5 will extend the results from Chapter 4 by not only analysing registry data and safety notices, but also safety problems identified in the peer-reviewed literature and from manufacturers' websites. The frequency of safety problems will be assessed for a random sample set of ten hip arthroplasty stems, ten hip arthroplasty cups, and ten knee arthroplasty implants to also obtain an estimate of the percentage of implants without safety concerns in any of these data sources.

In **Chapter 6**, multi-registry data will be used to validate the ODEP-rating, using revision risks of total hip and total knee arthroplasty implants across nine European and non-European registries. These results will show if the ODEP-rating could be used across countries to provide evidence on the safety and performance of total hip and total knee arthroplasty implants even if based originally on data obtained from another country.

Understanding and identifying differences in patient characteristics is important to ensure fair comparison of implant performances, given that these characteristics are known to influence the risk of revision. Hence, in **Chapter 7**, multi-registry data will be used to assess differences in patient characteristics of patients receiving the same total knee arthroplasty implants in different registries. If patient-mix differs across countries, this should be taken into account for a fair comparison of safety and performance regarding specific implants across registries.

In **Chapter 8**, national Dutch registry data will be used to assess whether the occurrence of revision surgery can be used for quality assessment to judge hospital performance following primary shoulder arthroplasty. In addition, the extent of between-hospital variation in revision following primary shoulder arthroplasty in the Netherlands will be assessed, both overall and for specific revision indications to guide quality improvement initiatives and to improve shoulder arthroplasty performances.

Chapter 9 includes a summary, general discussion, and offers some future perspectives.

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