The value of registry data in the clinical evaluation of medical devices

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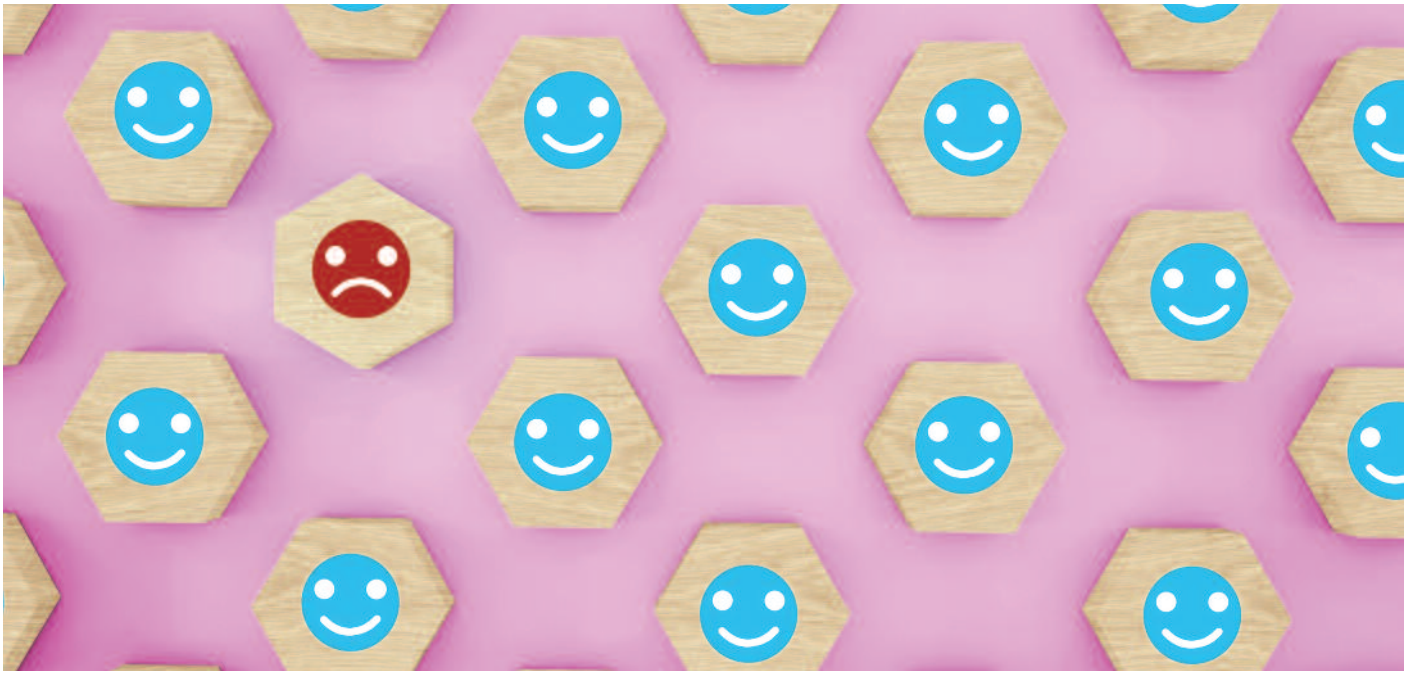
Abstract

Medical device manufacturers must continuously evaluate all clinical data available for their products marketed in Europe. With the European Medical Device Regulation 2017/745 coming into force in May 2021, manufacturers are required to assess available implant registry data as part of the clinical evaluation process. This new requirement will necessitate a closer collaboration between industry and registries to evaluate the safety and performance of high-risk devices. Medical writers should be aware of existing implant registries, understand what characteristics make a registry suitable to support regulatory requirements, and recognise both the value and the limitations of registries as a source of clinical evidence.

Patient registries provide a rich source of data on specific diseases, conditions, treatments, and exposures. Registry data are used to evaluate real-world treatments and outcomes, compare safety and effectiveness of treatments, monitor long-term safety, identify risk factors, and to assess quality in health care systems. Although randomised controlled trials are considered the gold standard for evaluating most medical treatments, it is not always feasible or ethical to carry them out on medical devices. Registries are increasingly seen as a supplement to data from randomised clinical trials, and in some cases, may be the only feasible approach to evaluate the long-term safety of some implantable devices.

The push to make better use of registry data for device surveillance increased as serious concerns about medical device safety came to light in 2012, specifically around the use of non-medical grade silicone in breast implants by Poly Implant Prothèse. This led the European Commission and EU countries to establish a joint action plan (Joint Plan for Immediate Actions under existing Medical Devices Legislation).[1] One of the five "immediate actions" was to support the development of implant registries that could identify safety issues and allow for long-term monitoring of safety and performance. Further implant safety issues making headlines in recent years, such as those related to metal-on-metal hip implants and vaginal mesh, only increased the pressure for heightened oversight and surveillance of medical devices, including calls for compulsory registration of all implantable devices.[2]



The European Medical Device Regulation (MDR) 2017/745 is the first regulation to include a specific requirement to evaluate registry data.[3] Article 108 of the MDR encourages the establishment of registries and registry networks based on common principles that enable the collection of comparable data on the long-term safety and performance of devices. It also suggests that registries contribute to traceability of implantable devices. In addition, the MDR requires both manufacturers and notified bodies to consider registry data as part of their obligations. Annex III (1.1 (a)) lays out the requirements to consider relevant databases and registries as part of post-market surveillance plans, while Annex VII (4.11(h)) requires an assessment of data from registries to be considered for re-certification by notified bodies.

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What is an implant registry?

The International Medical Device Regulator Forum defines a medical device registry as an "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)."[4] Registries use observational methods to collect standardised data on a population defined by a specific disease or condition (e.g., multiple sclerosis registry) or treatment with a specific product or procedure (e.g., arthroplasty registries). They may operate internationally, nationally, regionally, or at a single healthcare institution.[5] Many implant registries are led by professional medical societies or consortia. Implant registries collect more than just information about implants and include detailed information about patient characteristics and clinical outcomes.

Identifying implant registries

Keeping a complete and up-to-date overview of all operating implant registries is challenging. Generally well-established and long-standing national registries, such as the Swedish Knee Arthroplasty Register operating since 1975, the NJR (National Joint Registry) since 2002 in the UK, or SIRIS (Swiss National Joint Registry) since 2012, are easy to identify and will have the most valuable data in terms of quantity and quality. Smaller and newer registries may be identified through professional medical societies. Systematic reviews have been undertaken to map the implant registry landscape in Europe.[6,7] In 2013 researchers identified 101 implant registries in Europe and found that most are concentrated in the fields of cardiology (38 registries) and orthopaedics/arthroplasty (29 registries).[7]

A later review published in 2017 identified 24 hip and knee replacement registries in Europe.[6] Registries dedicated to other types of devices were less common: pacemakers and heart stents, breast implants, cochlear implants, insulin pumps, tubes, other stents, ophthalmological devices, brain stimulation/shunts, sacral neuromodulation, drug depots, and dental implants.[7] Another approach to identifying an appropriate registry is to search a registry of patient registries. The EMA inventory of registries maintained by the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance)[8] and the cross-border PARENT (PAtient REgistries iNiTiative)[9] list of registries of Europe are two such initiatives that aim to increase transparency, avoid duplication, and promote collaboration among registries.

What kind of data can implant registries supply?

Registries can supply data at the level of the patient, implant, healthcare provider, and healthcare clinic, all factors that can influence clinical outcomes. Typical types of data collected include patient demographics (e.g., age, sex, comorbidities), procedure details (e.g., type of surgery, surgical approach, surgery duration), clinical data (e.g., indication, diagnosis, previous interventions), patient follow-up, adverse events, and implant details (e.g., UDI-DI [Unique Device Identification-Device Identifier] and device characteristics). However, more variables are not necessarily better, and the overall burden on data providers needs to be considered. Registries that collect fewer variables with an easy and quick procedure may better ensure the continued motivation of the data providers and a higher level of data quality. When assessing the appropriateness of an implant registry as a source of clinical evidence, the use of harmonised implant categorisation, patient-reported outcomes, and the ability of the registry to link to other data sources are especially important aspects to consider.

Implant data

Historically, registry data collection focussed on treatment procedures and outcomes in clinical files and patient records. With increasing use of implants, the focus shifted to device-related outcomes. To enable meaningful comparisons between similar implants, registries characterise each implant by collecting detailed information on product characteristics such as type, size, shape, material, coatings, or other important attributes. Several initiatives at the European level as well as globally have led to harmonised classification systems for orthopaedic implants, an important step to enable comparisons between registries. The implant library developed by the EPRD (German Arthroplasty Registries) and adopted by the NJR,[10,11] and the ISAR (International Society of Arthroplasty Registries) International Prosthesis Library[12] are examples of such efforts. In the example of arthroplasty, the use of a standard implant classification to analyse revision rates and implant survival is a prerequisite for a registry to serve as an early warning system for implant failures.

Patient-reported outcomes

The patient's subjective evaluation of healthcare outcomes using patient-reported outcome measures (PROMs) has gained recognition in value-based healthcare assessment. In quality assessment studies, patients are asked to complete a PROM questionnaire before a surgical intervention – for example about levels of pain, difficulties in daily activities, work-related limitations due to a health issue, and effects on social activities and family. After surgery, the same questionnaire completed by the patient at a specified follow-up time or multiple times (e.g., at 6 months and 1 year) is compared with the baseline measures to assess if the intervention was successful. Many registries are incorporating PROMs and recognise that these outcomes complement the clinical outcomes.

Enriched data through linkage

Data collection for registries adds to the administrative workload of health workers, and registries should be designed with only the

minimal information needed. Registries that are able to capture identifying patient information, where legal regulations and informed consents allow, enable future linkage to external datasets and reduce the burden on the registry data provider. For example, information about a patient's vital status (i.e., dead, alive, emigrated, or unknown) is crucial to calculate accurate revision rates in arthroplasty but is generally not available in registry data. Linkage of registry data with routinely collected administrative data, like mortality data, can overcome this limitation. Linkage to other types of datasets enrich the registry data and can facilitate analyses of important topics such as cost-effectiveness. Furthermore, electronic patient records or data of healthcare insurances are rich sources of information for quality assessment and research.

Suitability of implant registries for regulatory submissions

The availability of relevant data from a registry is just one aspect to consider when assessing the suitability of a registry to provide clinical evidence. The International Medical Device Regulator Forum Registry Working Group has defined 15 registry requirements, grouped into six elements, to assess the suitability of registry data for regulatory submissions (Table 1). The importance of each element is weighted differently depending on the intended use of the data. For example, the use of controlled vocabularies is recommended for post-market surveillance, while it is highly recommended for data intended to support an initial device approval or indication expansion.[13] Additional aspects that merit consideration are the completeness of data collection, transparent quality assurance processes, a clear policy for data access and sharing, and registry sustainability.[14]

An example – the Swiss National Implant Registry

SIRIS began registering hip and knee implants in September 2012 and is now the largest implant registry in Switzerland, with data collection supported by 186 healthcare institutions. Participation is compulsory for all hospitals and clinics performing knee and hip arthroplasties. The registry included 90%–92% of all hip and knee replacement procedures occurring in Switzerland, according to the most recent coverage estimates.[15] In the SIRIS 2019 annual report, implant types and brands have been compared for the first time using an implant library based on product catalogues from industry partners. In arthroplasty, the implant revision rate is the main outcome of interest. A revision procedure occurs when a patient's primary hip or knee primary implant is replaced by new components.

Figure 1 shows an example of the kind of analysis that can be performed with registry data with sufficiently detailed implant data collection. The funnel plot shows the 2-year revision rates for each participating health service unit by volume of performed operations. This analysis identifies clinics with revision rates outside of the expected variability by chance. A second type of analysis of specific product brands can identify "outlier" devices or device combinations that have a higher than expected revision rate than similar benchmark devices (Figure 2). However, because registries use observational study methods, many factors could contribute to an outlier status such as patient selection, case-mix, surgical technique, surgeon experience, and health service characteristics. The initial analysis shown in Figure 2 provides an alert that initiates a more in-depth analysis of the underlying cause of a poor outcome.[16]

Challenges with implant registry data

There are many challenges associated with registry data collection, and many are not limited specifically to implant registries. Case coverage, completeness, and data quality are relevant for all types of registries. High quality medical device data collection poses a unique challenge to implant registries as well as disease registries that attempt to collect implant data.

Coverage and completeness

To answer questions about quality of health care treatments or safety of medical devices using registry data, careful evaluation of potential sources of bias is paramount. High external validity, especially when compared with randomised clinical trials, is an important advantage of registries. Results from registry data are

Table 1. Registry elements affecting the suitability of clinical data for regulatory use

Element	Registry requirements
Governance	• Transparent governance structure and processes
Quality management system	• Legal requirements for data collection and handling are met • Information on patient data protection • Policy on access to data • Essential information available for verification (e.g., by competent authority, notified body)
Data gathering	• Relevant variables • Unambiguous device identification (e.g., UDI system) • Ability to link with other data sources • Use of controlled vocabularies • Use of harmonised minimum data model
Data storage	• Security protection against hacking, altering, deleting, or stealing data
Methodology/data analysis	• Conduct of analyses across different types of analysis frameworks • Data interpretation
Transparency/display/distribution	• Publicly available reports; report frequency and content • Publicly accessible website and web-reporting

Adapted from the International Medical Device Regulator Forum Registry Working Group.[13]

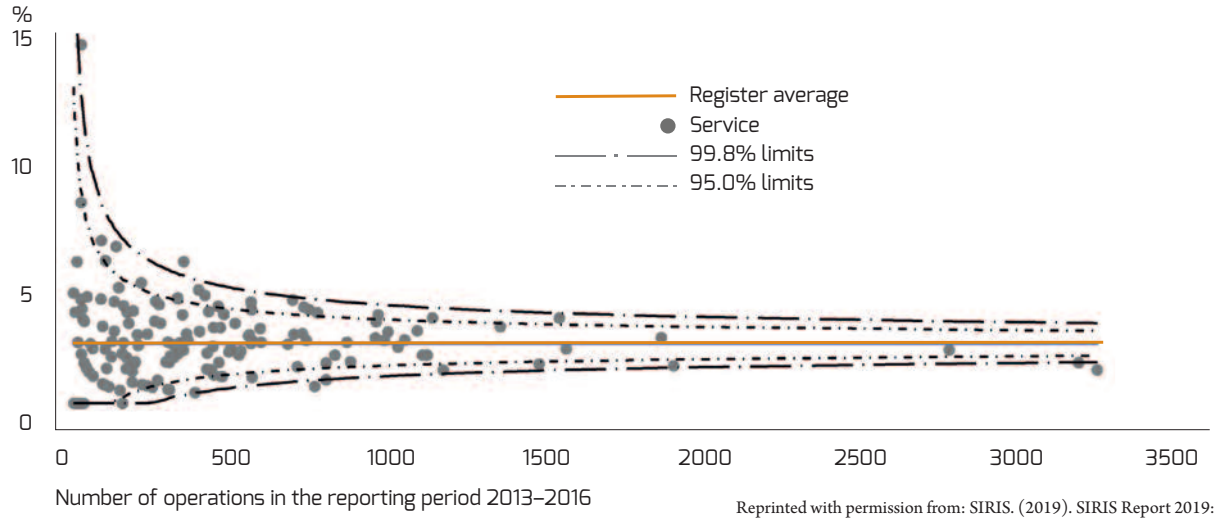

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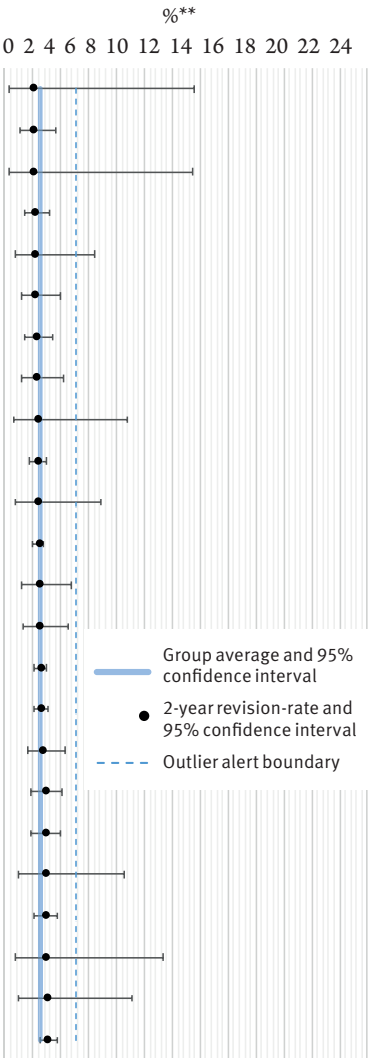
Figure 1. Example clinic analysis from SIRIS: Two-year revision rate of primary total hip arthroplasty by health care service

Combination	N revised	N at risk*
Exception + Betacup	1	50
Fitmore + RM pressfit vitamys	11	551
Harmony + April Ceramic	1	50
AMIStem + Versafitcup System	21	992
Alloclassic + Alloclassic	3	142
SL-plus + HI	10	468
Polarstem + Polarcup	19	882
SBG + R3	9	405
Corail + RM pressfit	2	88
Quadra + Versafitcup CC Trio	51	2278
Optimys + Allofit	3	134
Corail + Pinnacle	167	7124
Exception + Avantage	8	339
Quadra + Versafitcup System	10	416
AMIStem + Versafitcup CC Trio	145	5796
Avenir + Allofit	105	4164
SL-Plus + EP-fit	15	581
CLS + Allofit	25	895
CLS + Fitmore	28	1019
Corail + Allofit	3	107
Twinsys + RM pressfit vitamys	41	1485
Accolade + Trident	2	68
Exception + Exceed	3	99
Fitmore + Allofit	100	3301



* Number of patients with at least two years follow-up (i.e. primary prosthesis in 2012–2016).
** Rates ajusted for effects of mortality and emigration.

Figure 2. Example benchmark analysis from SIRIS: Two-year revision rates of uncemented stem-cup combinations used in primary total hip arthroplasty (2012–2018).

Reprinted with permission from: SIRIS. (2019). SIRIS Report 2019: Annual Report of the Swiss National Joint Registry, Hip and Knee, 2012 – 2018. [15]

generalisable if several conditions are met. A national registry needs to include all health services in the country delivering the treatment in focus. Underrepresentation of some areas or types of health services may introduce bias. Within a healthcare facility, all procedures meeting the inclusion criteria for the registry need to be recorded for full coverage. Excluding services or complex cases leads to bias in the analyses, interpretation of data, and generalisability. To calculate many outcome measures (e.g., the revision rate from arthroplasty registries), detailed knowledge about the registry coverage is vital. For example, if an implant revision surgery is performed in a clinic that does not record the operation in the registry, the revision rate will be underestimated. Another condition for unbiased analyses is the completeness of data. For the complete recording of implants, smart implant interfaces are needed. The type of operation (e.g., total hip arthroplasty) defines the expected type and number of implants and can be tracked during the scanning process. Warnings and error messages help to ensure that all expected implants for each case are captured.

Data quality

Several measures help to ensure and evaluate the quality of data and results:

1. use of reference data, sales figures, insurance data, or routinely collected administrative data to estimate the coverage of the registry,
2. precise definitions of inclusion and exclusion criteria for the registry, and
3. thoughtful design of electronic data capture forms, with precise definitions of variables, ranges of valid data, distinct categories of answers, mandatory and optional fields, and handling of potential missing data.

Measures for high registry data quality, coverage, completeness, and correctness can be implemented during different phases of the registry data capture process. Variable definitions, inclusion and exclusion criteria, and validation rules are defined before the data entry. During data entry, registry system rules provide warnings and errors, and first level support teams help with completing data entry forms. After data entry, automated monitoring routines and plausibility checks help detect potential errors or inconsistent data entries. Finally, for registries with sufficient funding, monitoring visits in the clinics and standardised audits verify the correctness of the data entered by comparing the source information in the clinical records with data captured in the registry.

Implant libraries

To access usable data for manufacturers to fulfil clinical evidence requirements, many registries do not have sufficiently detailed data collection to enable sophisticated analyses of specific implants. For example, some registries may collect data on general types of medical devices or implants used (e.g., plates, screws, external fixator) but not details that allow identification of a specific brand, model, or reference number. Another challenge is implementing a standardised categorisation of implants so that data may be compared across registries. Recent international congresses and meetings, for example the International Society of Arthroplasty Registries conferences, have advanced the discussion about standardisation and harmonisation of implant libraries. This led to agreements between the NJR in the UK and the German EPRD to harmonise their existing implant library definitions. Keeping these libraries up-to-date and accurate requires commitment from industry, with manufacturers needed to classify existing and newly marketed products according to a standard system with sufficient granularity that meaningful data analysis can happen.

In the future, the standardisation of implant libraries will reduce the administrative burden for manufacturers who provide implant catalogues with different categories and levels of granularity for different registries in many different countries. Ideally, implant registries may update their implant libraries using comprehensive implant data warehouses such as EUDAMED (European Database on Medical Devices) or other international databases. Unfortunately, local legal regulations leading to products sold in some but not other countries and challenges in standardisation processes hamper the development of international implant registries.

It is important to ensure that registries used to support regulatory requirements are well designed to produce valid data.

Conclusion

An increasing focus on the role and value of registries has led to steps to encourage better integration of registry data into regulatory decision making.[16,17] This effort requires the collaboration and input of all registry stakeholders, including patients, health care providers, professional societies, registry custodians, researchers, reimbursement bodies, public health and regulatory bodies, and the medical device industry. It is important to ensure that registries used to support regulatory requirements are well designed to produce valid data. The medical writer will play an important role in communicating clinical evidence on devices generated from registry data.

Disclaimers

The opinions expressed in this article are the authors' own and not necessarily shared by their employers or EMWA.

Conflicts of interest

The authors declare no conflicts of interest.

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