Biomedical Alliance in Europe

ESC European Society of Cardiology

BioMed Alliance, ESC & EFORT Report

Workshop Medical Device Registries

17 June 2019

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1. Introduction

On 17 June 2019, the BioMed Alliance, the European Society of Cardiology (ESC) and the European Federation of National Organisations of Orthopaedics and Traumatology (EFORT) jointly organised a workshop in Brussels bringing together leading scientists and key representatives in regulatory affairs for an open discussion on Medical Device Registries[1]. The workshop focussed on the regulatory context, best practices and on future directions towards identifying what role clinical registries may play in informing regulators' market surveillance activities and establishing a possible "common framework" for EU registries responding to the needs of regulators, patients, physicians and industry alike.

The discussions took place within the context of the new Medical Device Regulation which will entail strengthened controls before devices enter the market as well as increased post-market surveillance.

Because they contain such a wealth of information and are continuously updated, attendees concluded that registries can play a key role in providing clinical evidence to regulators for the assessment of medical devices.

2. Regulatory Framework

General introduction to the Medical Device Regulation (MDR)

The EU introduced two new regulations to revise and strengthen the regulatory framework for medical devices and in vitro diagnostics[2]: the Medical Devices Regulation (Regulation (EU) 2017/745) or MDR and the In Vitro Diagnostics Regulation (Regulation (EU) 2017/746) or IVDR. The regulations propose reinforced rules for clinical evidence and market surveillance.

Overview of the requirements for post-market clinical evidence under the MDR – Dr. Paul Piscoi

In order to place a device on the EU market under the MDR, manufacturers will have to establish an incident investigation and reporting system (Article 87), a post-market surveillance system (article 10 and 83 onwards) and an approved plan for post-market clinical follow-up (article 32.2). This includes a new provision that stipulates the establishment of a risk-management system which continuously provides up-to-date information throughout the lifecycle of devices (Annex 1, p3) which intends to timely identify, prevent and address risks quickly.

Post-market surveillance includes all activities of manufacturers to proactively collect and review experiences with devices placed on the market. This includes setting up a post-market surveillance plan (Article 84) and issuing reports summarising results and conclusions of analyses of post-market surveillance data, a rationale and description of any preventative and corrective actions taken. These include post market surveillance reports (article 85) for class I devices and class A and B IVDs (made available to competent authorities on request) and periodic safety update reports (article 86) for Class IIa, IIb and class III devices and class C and D IVDs.

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[1] Registries are defined as: ""..organised systems that use observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure that is followed over time" (EMA, 'Patient Registries, retrieved on: 22 July 2019 from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries)

[2] European Commission (2019), Medical Devices: New regulations https://ec.europa.eu/growth/sectors/medical-devices/new-regulations_en

Clinical data is defined as information concerning safety or performance that is generated from the use of a device and is sourced from the following: clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up.

"The clinical evaluation and its documentation shall be updated throughout the life cycle of the device concerned with clinical data obtained from the implementation of the manufacturer's PMCF plan in accordance with Part B of Annex XIV and the post-market surveillance plan referred to in Article 84." (Article 62(11).

The post-market surveillance plan addresses the collection and utilisation of available information, in particular databases and/or registers and information, including feedbacks and complaints, provided by users, distributors and importers.

Data collection and analysis:

There are three sources of information foreseen in the MDR:

- post-market surveillance system of the manufacturer
- periodic safety report by manufacturers
- analysis and trends in the vigilance data of EUDAMED

Device registers (slide 23)

Under article 108 of the MDR, the European Commission and the Member States are urged to promote the establishment of registers and databases for specific types of devices.

"**Article 108: Device registers and databanks**

The Commission and the Member States shall take all appropriate measures to encourage the establishment of registers and databanks for specific types of devices setting common principles to collect comparable information. Such registers and databanks shall contribute to the independent evaluation of the long-term safety and performance of devices, or the traceability of implantable devices, or all of such characteristics."

According to Paul Piscoi, registries need to have common principles to collect comparable information, and this should be encouraged. Registries may help to ensure the long-term safety and performance of medical devices. Manufacturers are allowed to submit data collected independently by academic bodies or scientific associations.

Registries are only mentioned in Annex VII as a form of evidence for re-certification 4.11 H

Expert Panels

The new regulations propose the establishment of expert panels, which will 'support the assessment of specific high-risk devices and contribute to the prospective improvement of the overall framework by advising the Commission, the Medical Device Coordination Group, Member States, Notified Bodies and manufacturers.' [3]

Dr. Paul Piscoi explained that as part of the conformity assessment procedures of high-risk devices, so class III implantable and IIb active devices aimed at administering and removing pharmaceuticals, the EC is preparing the creation of scientific panels. Their role will be to look at the clinical evaluation (created by manufacturers) and clinical evaluation report (created by Notified Bodies) along with the

[3] https://ec.europa.eu/docsroom/documents/36041

clinical data and give an opinion on the quality of that clinical data. So, the EC is establishing a number of scientific panels and sub-panels and a call was launched in autumn 2019.

EUDAMED

There are a number of elements in the new medical device regulation aiming to ensure transparency. One such element is the central database, EUDAMED. According to Paul Piscoi, clinical evaluation summaries will be made available, including for those studies that are temporarily halted or permanently stopped. EUDAMED is supposed to assist the implementation of the directives and will facilitate information exchange to help authorities with their market surveillance activities. A traceability system will be set up which will allow the tracking of all medical devices. To protect intellectual property, most of the information in the database will be available only to competent authorities in member states and Commission officials, but part of the information will be available to the public.

Information on EMA requirements for approving independent registries

The European Medicines Agency (EMA) is responsible for regulatory affairs related to medicines, and it has officially approved registries for use in post marketing surveillance of drugs. Daniel Zondag, from the Pharmacovigilance and Epidemiology Department at the EMA, stated that the EMA started its patient registries initiative in 2015. One of its aims is to facilitate the use of disease registries by introducing and supporting a systematic approach to contribute to the benefit-risk evaluation of medicines. The EMA organised a series of specific workshops and developed a strategy related to registries.

2 key components of the registries strategy:

- Promote dialogue between regulators, companies and registry holders to identify opportunities and barriers in disease registries.
- Provide guidance to clarify methodological concepts and regulatory requirements, because there is a lot of confusion about terminology used by regulators and companies.

During a workshop with stakeholders, the EMA identified some lessons that should be taken into account in relation to registries:

- A set of common core data elements is crucial.
- Data quality: the implementation of attested data control quality systems is important.
- Governance: collection and reporting of adverse events, needs to be defined and described in a study protocol. There needs to be a system in place that strongly encourages physicians to report suspected adverse events to national pharmacovigilance agencies.

According to Daniel Zondag, the use of disease registries can be supported in the following ways:

- Operational and methodological guidance on the use of disease registries from a regulatory perspective
- The Qualification procedure (advice given by scientific advice working party)
- Scientific advice on PASS/PAES study protocol using registries, e.g. joint collaborative studies
- The EMA has recently started an inventory of disease registries, called the ENCePP Resource database
- Facilitation of interactions between regulators, industry and registry holders at an early stage of product development and during the entire life cycle of a product

Dr. Zondag explained that there are several opportunities during the development process and authorisation procedure where registries for post-authorisation monitoring of products can be used, as well as in the early stages of product development, and in the evaluation and the post-authorisation phase. It is important that companies initiate discussions with regulators at the earliest possible moment, so relevant registries, the right data source and additional data that may need to be collected can be identified.

Under the EMA qualification procedure for registries, registries can receive official EMA approval. The qualification procedure entails scientific advice on the acceptability of a specific method in the context of research and development of pharmaceuticals.

- Qualification advice: advice on how to improve the quality of the specific method in order to get a qualification opinion
- Qualification opinion: defines acceptability of a specific method for a specific purpose, also applied to patient registries. The opinion is provided by the Committee for Medicinal Products for Human Use (CHMP) on the basis of advice provided by the Scientific Advice Working Party (SAWP).

According to Dr. Zondag, two registries have received a qualification opinion:

- European cystic fibrosis society patient registry (ECFSPR)
- European Society for Blood and Marrow Transplantation Registry (EBMT)

The qualification opinion provides certainty that the data source is of a certain quality, and for registries it can facilitate contracts with companies that use registries for regulatory purposes.

3. Examples of Best Practices

Swedish national registries and system (such as SWEDEHEART / orthopaedic, etc); Added benefits – randomised registry trials

Registries in Sweden

Prof. Jonas Oldgren, Executive director at the Uppsala Clinical Research Center (UCR) explained that there are six National Competence Centers and 106 National Clinical Quality Registries in Sweden, which continuously collect individualised data on symptoms, diseases, medical interventions, procedures and outcomes after treatment within regular healthcare. UCR is the biggest competence center and it supports more than 20 clinical registries in Sweden.

The registry system is jointly funded by the government and all 21 County councils (public health care providers) and each registry is led by a steering committee.

Participation in the registries is voluntary, nonetheless in the majority of registries all hospitals participate. Swedish registries have a long tradition and some registries, such as one in orthopaedics, have been running since the 1970s. Prof. Oldgren argued that registries should be actively used for health care improvement, continuous learning, research and knowledge management, and life science collaborations.

SWEDEHEART

Prof. Oldgren presented the example of SWEDEHEART, a cardiology registry that is internationally one of the most renowned Swedish registries. SWEDEHEART went online in 2009, is completely web-based and covers many cardiovascular diseases. It has 100% coverage of all hospitals with coronary

care units. Data is directly entered by operators or healthcare professionals and there is a direct link with population registries.

The registry provides feedback to staff, e.g. to assist in providing guidelines and recommended treatments. SWEDEHEART provides feedback to leadership comparing the hospital to the 20 best hospitals in Sweden per variable. The registry also provides feedback to the patient and to the public.

There are also a few mandatory registries in Sweden and information is based on the personal identification number of patients. Data from clinical quality registries can be combined with electronic health records, hospital discharge registries, outpatient discharge registries and drug prescription databases. This data is connected for e.g. research and treatment purposes.

Data from the SCAAR registry, the coronary angiogram registry (angioplasty registry) provides information on early detection signals on increased risk of myocardial infarction in patients with drug-eluting stents. These stents were introduced to reduce restenosis. However, signals in the SCAAR annual report showed that they could lead to a higher risk of acute myocardial infarction and follow-up suggested that there was a 30% increased risk of death. A new generation of drug-eluting stents showed no increased risk of mortality.

Registry-based randomised clinical trials

However, Jonas Oldgren stated that it should be taken into account that observational data can be biased. A single center randomised clinical trial indicated that thrombus aspiration in ST elevation myocardial infarction significantly reduced the risk of mortality. However, data from the national registry showed different results and a higher risk of mortality compared to the single center study. So, they developed a new concept and conducted a registry-based randomised clinical trial.

Registries can help in the execution of clinical trials by:

- Identifying eligible patients
- Assisting with and collecting electronic consent forms
- Randomisation
- Collecting baseline and procedure characteristics (CRF)
- Identifying clinical endpoints (endpoint detection)
- Reporting clinical outcome events

The registry-based randomised trial in this specific case had neutral results and data did not show a reduction in the risk of mortality but it did indicate a higher risk of stroke. Therefore, it helped to demonstrate that the data from the single centre study was unreliable.

In short, registries in Sweden are publicly funded, have a wide coverage and provide an important contribution to the provision of health care. Registries are gaining input from and are used to evaluate scientific evidence, basic research, new treatments and clinical trials, diagnostic methods and quality improvement.

European cardiology disease-based registries

Dr. Aldo Maggioni, director at the ANMCO (Italian cardiologist association) research centre and scientific coordinator of the European Society of Cardiology (ESC) EurObservational Research Programme (EORP), presented developments on establishing cardiology-disease based registries at EU level.

The EORP was launched in 2010 and according to Dr. Maggioni it aims to be representative for Europe. It is managed by the European Heart House in an independent way, but there is cooperation with industry. The main objectives of the programme are to evaluate the use of ESC guidelines in Europe and then to implement an educational programme to fill in the gaps. They foresee to establish a registry two years after the release of guidelines to evaluate their implementation. The registry provides outcome measurements and will be linked with the ESC Atlas.

Under the EORP, registries have been conducted for common diseases, rare diseases and in relation to interventions and prevention. For example, an important registry is the one for pregnant women with structural heart disease, which has enrolled 6000 women. Dr. Maggioni explains that information in the registry is of vital importance since trial data for their situation does not exist.

The ESC Heart Failure registry contains data on 12,440 patients from 21 countries. This registry aims to enhance understanding of the rate of application of recommended treatments. Results showed that while the recommended drugs were generally used, the recommended dosage was not always followed. There is a bigger gap between guidelines and clinical practice related to devices, which can be explained due to differences between hospitals, and healthcare systems. The registries have also been used to evaluate the effect of adherence to guidelines on mortality.

European device registries for orthopaedics implants, hip fracture, etc; International collaborations with NARA, ICOR; use of PROMs

According to Prof. Rob Nelissen, Chairman of the Network of Orthopaedics Registries of Europe (NORE), registries can not only benefit regulators and manufacturers, but also they can help clinicians to improve patient care.

Orthopaedics registries in e.g. the UK, the Netherlands and Scandinavian countries contain high-quality data because they have 100% coverage and 99% completeness. Prof. Nelissen explained that at the moment, clinicians fill out data in different systems but that it would be better if there is one central national system in order to compare results within a country. Ideally the same format should be used between countries in Europe for comparison between countries. Validation is also needed on what constitute high quality systems. Data collection needs to be conducted properly, otherwise it is 'garbage in and garbage out' (poor data collection leads to bad data quality).

Registries contain observational real-world data and play an important role in tracking implants. Data in registries can be used as a benchmark for a certain implant and the average revision timeline. In orthopaedics it is important to measure the survival of the implant to help identify the right option for patients. Traceability is also very important, when there is a recall of a certain device or implant, clinicians can follow up.

Registries can also be used to evaluate performance of healthcare providers. They have the potential to identify implants or even hospitals and surgeons that function below average. However, caution is necessary when interpreting data, some surgeons or hospitals specialise

in riskier surgeries and thus have a lower score. Data, if interpreted properly, can be used by doctors to improve their own performance.

Prof. Nelissen is hopeful that the effective use of registries will lead to improved patient care and less exposure to mediocre or badly functioning implants. He argues that making data publicly available will improve healthcare. Clinicians should base their decisions on clinical evidence and registries may help inform these decisions.

Diabetes registries (devices in diabetes, insulin pumps)

Prof. Reinhard Holl is active within the European Association for the Study of Diabetes (EASD) and presented data from three registries related to diabetes:

- The German DPV registry containing data on 550.000 patients
- The SWEET registry, a worldwide registry for paediatrics containing data on 58,110 patients. It started as EU public health programme in 2008.
- The DIVE Registry, a German registry evaluating the quality if care for patients with diabetes.

A large amount of the patients included in registries use pumps to treat their diabetes, and the registries thus provide a good overview of pump use among diabetes patients. Prof. Holl argues that pump use started around the turn of the century and has been increasing in the last years. In the beginning, pumps were mainly used on adults but since 2005 pump use among paediatric patients has been proportionally higher.

Registries allow to narrow down the perspective and look at specific aspects of care. For example, the correlation between different factors and characteristics (e.g. geographic location, age, gender and socio-economic status) and pump use can be demonstrated by looking at registries. In addition, registries can provide information on the safety of insulin pumps, and on the advantages and disadvantages between the use of insulin pumps and injections. They can also provide information on specific types and brands of devices.

Data from registries show that the current use of diabetes technology is rapidly increasing. It is essential to monitor safety and efficacy, and registries can play a role in the post-market surveillance of these technologies. Moreover, the development and use of new technologies will carry new risks which will have to be monitored. Data can help analyse specific devices and allows for the continuous modification and improvement of devices.

Age-related registries, such as in paediatrics

Prof. Dominique Haumont, coordinator of the International Benchmarking and Evaluation Programme eNewborn, provided key insights on neonatal registries. Prematurity is one of the major health problems in infants and neonates, and it has both short-term and long-term consequences. This group of patients has a high risk of mortality and thus registries can provide essential information on the actions that can be taken.

The data can have an important impact on clinical practice and can also show the effects of an evolution of a certain intervention. Moreover, the data in the registry has shown that not

only the more premature a patient is the more likely they are to die, but also the more growth-retarded a patient is the more likely they are to die.

Prof. Haumont explained that there are many practical and administrative barriers to establishing and running registries. She argued that when setting up a registry, it is important to effectively identify the study population, to decide the appropriate items to include, to have a precise definition of these items, to have a feasibility of data mapping, ensure sufficient motivation of the unit to send the data correctly, to create user-friendly software and ensure sustained funding.

The eNewborn network gradually developed, Prof. Haumont was first responsible for the national Belgian database for neonates. Because Belgium is such a small country and the number of premature babies in the registry was limited, she and her team started a partnership to gain a bigger control group. In the past three years, they built up a database of almost 40.000 patients. Units can be linked, and the database allows for filtering and e.g. only looking at very specific populations.

The cooperation, and thus the bigger control group, can help accelerate research. For example, Prof. Haumont demonstrated that when one would look merely at the database in Belgium, for infants delivered at 25 weeks gestational age it would take between 7-10 years to demonstrate the impact of an intervention but with the whole network it only takes 1 year to see whether it was effective. For bronchopulmonary dysplasia in neonates it would take 30-50 years if one would only look at Belgium, whereas in the entire network it would take 3 years to identify its impact on morbidity.

Certain challenges persist, for example if the IT system in each hospital is different, but the managers of the registry have taken measures to facilitate data entry. Not each country has centralised electronic health records, and therefore the team managing the registries would have to contact each hospital individually. Moreover, due to General Data Protection Regulation (GDPR) the whole security structure of the registry had to be rethought, even though it was already of good quality. There are some specific difficulties, under the GDPR data sharing across borders must be done between official organisations. Therefore, eNewborn will have to move the IT structure in Belgium to an official database institution. The team has to identify which umbrella organisation would be able to do that job.

Regarding funding, the Belgian network is sponsored by the Belgian Ministry of Health. For the eNewborn international project, Prof. Dominique Haumont applied to a foundation for a grant which was used to set up the platform. The costs are increasing in order to adapt to new regulations such as the GDPR, so Dominique Haumont is exploring how to fund it in the future.

So, with eNewborn, a successful and important European Evaluation Programme and Benchmarking Platform was established that is easily accessible and contains online or mapped uploaded data that is close to population-based database. In the future, the programme will expand relationships with stakeholders in the field to continue working towards its objectives;

- To secure sustainability of the network and to increase participation
- To monitor quality of care
- To enclose parents in the vision of the network
- To incorporate real world and big data
- To prioritize security and GDPR compliance
- To become a major partner in neonatal health care actors

4. Key principles and objectives of registries

- Responsibility of all healthcare professionals involved in direct care
- Consent for implantation should include consent for follow-up
- Universal coverage / comprehensive inclusion
- Run independently of manufacturer
- System of public funding / independent support
- Full transparency / independent reporting / with public access
- Embedded in routine health care, incorporated into electronic health record
- Genuine long-term and complete follow-up
- Data controlled by clinical teams with ICT and statistical support
- Common data fields, variables, across registries for any particular class
- Anonymised/pseudonymised data can be shared across national borders
- Need for automated surveillance and reporting systems for safety signals to be transmitted to regulators / EUDAMED

5. Next steps

- Guidance for individual clinicians and/or patients: how to report incidents and concerns (to manufacturer, notified body, MS regulatory agency, Commission?)
- Guidance to clarify provisions and exemptions with respect to the EU General Data Protection Regulation (seek advice from DG JUST?)
- Public funding or other sustainable mechanism
- National facilitators? Expert support for hospitals?
- Links with EMA, hybrid devices, extrapolations for new drugs ..?