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The Role of Massive Databases in the Post-market Clinical Follow-up of Medical Devices

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Abstract: With the application of new European regulations on medical devices in May 2021, the requirements for clinical evaluation have been strongly reinforced. Post-marketing clinical follow-up is now a key activity for manufacturers to keep their medical devices on the market. The use of material-epidemiology studies and real-life databases has multiple strengths and advantages. However, the weaknesses and limitations identified do not yet allow manufacturers (especially small and medium-sized companies) to fully utilize these tools for post-market clinical follow-up. Yet certain technological and regulatory developments already implemented, and to be implemented over time, suggest that these tools could play a crucial role in the clinical monitoring of medical devices in the future. In order to better define the future use of real-life data in post-market clinical follow-up activities, a comprehensive update of technological and regulatory surveillance is still required.

1 INTRODUCTION

Regulation (EU) 2017/745 on medical devices (other than in vitro diagnostic medical devices) has been in force since May 26, 2021 in all member states of the European Union. It was adopted to establish a rigorous, transparent, predictable and sustainable regulatory framework for medical devices. This framework must guarantee a high level of safety and health protection while promoting innovation (European Parliament and European Council, 2017).

Regulation (EU) 2017/745 constitutes a complete overhaul of the regulations governing the rules for placing medical devices on the market, making them available and putting them into service. Adopting these changes represents a real challenge for the different protagonists of the sector, particularly for manufacturers. The dimensioning of the clinical evaluation and the obligation for the manufacturer to ensure a post-market clinical follow-up integrated into its post-market surveillance plan are among the major changes brought by the new regulation. (Nicolas Martelli, 2019; Beata Wilkinson, 2019; Alan G. Fraser, 2020).

There are various methods to support post-market clinical follow-up. However, some methods do not always cover all the objectives of these activities. The use of real-life data is therefore essential for the clinical evaluation of medical devices.

Here again, various strategies for the use of real-life data are available to medical device manufacturers: while the implementation of clinical investigations is one of the most suitable means of generating clinical data to address targeted issues, the multiplication of data warehouses and the use of the latter could also make it possible to achieve these objectives without necessarily involving human beings.

The reflection carried out within the framework of this work concerns the following issues: "What is the current position of material-epidemiology and more particularly of massive databases in the post-marketing clinical follow-up of medical devices?" and "What are the prospects of using these tools in this field of activity?"

2 POST-MARKET CLINICAL FOLLOW-UP

According to Annex XIV, Part B, Paragraph 5 of Regulation (EU) 2017/745, post-marketing clinical follow-up *"shall be understood as a continuous process that updates the clinical evaluation"* and *"shall be addressed in the manufacturer's post-market clinical plan"* (European Parliament and European Council, 2017). The methods and measures used in post-market clinical follow-up activities are documented in a post-market clinical follow-up plan.

Post-market clinical follow-up activities *"proactively collect and evaluate clinical data from the use in or on humans of a CE marked medical device, placed on the market or put into service within its intended purpose"* (MDCG, MDCG 2020-7- Post-market clinical follow-up (PMCF) Plan Template, 2020). The results of these activities should help to achieve the following objectives:

- i) confirm the safety and performance of the medical device throughout its intended lifetime and cover the limitations identified in the clinical evaluation report;
- ii) detect unknown adverse effects, monitor them, and identify possible contraindications;
- iii) identify and analyze emerging risks based on the evidence;
- iv) ensure the acceptability of the benefit/risk ratio;
- v) identify any possible misuse or off-label use of the medical device

(Josep Pane, 2018; <https://www.qualitiso.com/scac-suivi-clinique-apres-commercialisation>, 2021).

The limits of clinical evaluation can only be identified when the context of the medical device's clinical use and its associated performances have been precisely identified. Indeed, identifying the limitations corresponds to an analysis of the sufficiency of clinical evidence performed through clinical evaluation. Upon conclusion of the clinical evaluation report, the manufacturer should be able to answer the following questions:

- i) Are there any unsubstantiated or partially unsubstantiated claims?
- ii) Is the benefit/risk ratio acceptable over the lifetime of the medical device?
- iii) What are the complications and other residual risks associated with the use of the medical device?

The implementation of post-marketing surveillance activities and more particularly post-marketing clinical follow-up activities depends on the answers to these questions and must make it possible, in the more or less long term, to cover the limits identified, otherwise the CE marking of the medical device could be jeopardized.

There are several ways of conducting post-market clinical follow-up activities. General methods and procedures (analysis of the scientific literature, feedback from congresses, etc.) have the advantage of being economical for the manufacturer, but generally do not make it possible to overcome all the limitations identified. Implementing specific methods and procedures for each medical device is therefore very often necessary to compensate for the lack of clinical evidence. Each method has its own advantages and disadvantages. This makes the post-market clinical follow-up strategy and planning even more complex.

3 REAL-LIFE DATA FOR POST-MARKET CLINICAL FOLLOW-UP

Material-epidemiology can be defined as follows: *"like pharmacoepidemiology, as a discipline that applies epidemiological methods and/or reasoning to evaluate, generally on large populations and over long periods of time, the effectiveness, risk and use of medical devices in real life"* (Equipe pédagogique DU, 2020-2021). Material-epidemiological studies are observational studies that make it possible to approach the reality in the field without disrupting the usual behaviors of prescribing, fitting and using the medical device by collecting real-life data. They can be prospective, retrospective or ambispective.

The collection of real-life data and the use of massive databases are now recognized in the European regulation on medical devices just as in Article 108 of Regulation (EU) 2017/745 *"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."* (European Parliament and European Council, 2017). This therefore suggests an acceleration in the use of

this type of study in the clinical follow-up activities of medical devices.

3.1 Real Life Data Warehouses

Bégaud et al. define "real-life data," as "data that are without intervention in the usual patient management arrangements and are not collected in an experimental context (which, notably, is the case with randomized controlled trials), but which are generated during the routine care of a patient, and which therefore reflect a priori current practice. Such data can come from multiple sources : they can be extracted from computerized patient records, or constitute a by-product of the information used for healthcare reimbursement; they can be collected specifically [...], or to constitute registries or cohorts, or more punctually as part of ad hoc studies; they can also come from the web, social networks, connected objects, etc." This definition is included in the more general definition of "health data" proposed in Article 4 of the General Data Protection Regulation (GDPR) and supplemented in Recital 35 of the GDPR (Ministère des affaires sociales et de la santé, 2016; Bernard Bégaud, 2017; Club de la Sécurité de l'information Français, 2019).

As a result, there are a multitude of data sources available to provide insight into questions related to the efficacy, safety, and use of medical devices.

To illustrate the wide variability of real-life data sources and processing possibilities, two typologies of real-life data repositories that can be used in manufacturers' post-market clinical follow-up strategy are presented below. It should be noted that these examples are not intended to be an exhaustive presentation of all the solutions available to manufacturers.

3.1.1 Practice Registries

Practice registers are integrated with the aim of evaluating, monitoring and improving practices. They are databases made up of standardized data (specifically entered to feed the registry), resulting from professional practices, most often relating to a specific theme. The collection and analysis of these data are widespread within professional organizations, learned societies or networks. The setting up of a practices register is orchestrated by a professional structure made up of peers who run the register and are responsible for:

- ii) the design of the register (this includes compliance with the regulations applicable to the collection and processing of the data collected and guarantees of confidentiality of the data relating to the patients and health professionals involved);
- iii) the quality of the data collected and the methodology for entering the data;
- iv) analysing and exploiting the data collected

(CNIL; HAS, 2014; Group_IMDRF_Patient_Registries_Working, 2016). Certain fields, such as thoracic and vascular surgery, orthopaedics and interventional radiology, are among those for which practice registers are frequently implemented (CHRU_Tours, 2021; Besse, 2020; Berghmans, 2020). However, as long as they comply with the regulations and methodology described above, these tools can be deployed in many fields of application, with the operation and constraints specific to each register.

Exploiting the real-life data provided by practice registries is part of the routine activities carried out by manufacturers in the context of their post-market clinical follow-up activities. Indeed, the periodic reports published within the framework of the bibliographic monitoring carried out by manufacturers, are a means of updating the state of knowledge on medical devices and the pathologies under evaluation. They generally feed the state of the art with, for example, data relative to the clinical conditions of use of medical devices (target population, indications, type of medical device or assembly preferred, etc.). In addition, some practice registries now offer services that allow a manufacturer to access aggregate data analysis reports for medical devices for which it is the legal manufacturer. That way, the manufacturer can use practice registry data as a source of clinical data specific to its medical devices.

However, the independent and often voluntary nature of this type of approach does not always allow for comparability of data between different registries (items filled in, methods of inclusion, granularity of information provided not always sufficient for the manufacturer to accurately identify the medical device used, etc). In addition, the data format and access restrictions generally do not allow the manufacturer to remove all uncertainties regarding the medical device of interest (aggregated data, access to manufacturer data only). Finally, the reports submitted reflect the results of device use as of the date of the report. This limits longitudinal follow-up.

- i) the theme of the register;

3.1.2 Health Data Warehouses

The main purpose of health data warehouses is to concentrate and guarantee long-term access to existing massive data relating to the medical care of patients, socio-demographic data, data from previous research, practice registers, etc. These data are exploited for research, studies or evaluations in the field of health. Massive data warehouses often make it possible to bring together data initially stored in different heterogeneous databases. Centralizing this information helps to:

- i) consolidate it,
- ii) guarantee its coherence and quality,
- iii) consult it in a transversal way,
- iv) identify it and also
- v) use it more easily by quickly constituting cohorts.

Unlike a targeted research project, study or evaluation (the aim of which is to respond to a specific objective limited in time), a health data warehouse corresponds to the constitution of a large database for which, in the long term, the data controller can envisage processing the data in several ways within the framework of different research projects. However, it should be noted that health data warehouses can only be created for the sake of public interest (CNIL; <https://www.cnil.fr/professionnel>, 2021; <https://www.has-sante.fr/>, 2021).

As examples,

- i) The National Health Data System, is a large-scale real-life data warehouse implemented to analyze and improve population health (SNDS) (<https://www.snds.gouv.fr/SNDS/Accueil>, 2021);
- ii) The implementation of hospital warehouses is increasingly frequent in order to concentrate, in a single data warehouse, a set of real-life data collected over a limited territory;
- iii) The constitution of personal data warehouses for the purposes of research, study or evaluation in the health field by specialized companies is also frequent.

Depending on the specificities of each data warehouse, access (direct or indirect) to manufacturers of medical devices is not always allowed. However, when this is possible, these tools offer a multitude of processing possibilities within the limits of each health data warehouse (data compartmentalized within the health data warehouse,

often significant and uncontrolled implementation time, inconsistency of data in case of absence of consolidation and monitoring process, relatively high cost of data exploitation for manufacturers, etc).

3.2 Current Strengths and Limitations of using Real-Life Data in the Activities of Post-market Clinical Follow-up

The use of massive databases on real-life data for post-marketing studies appears to be a solution that has the advantages over clinical investigations of consuming fewer financial and human resources, being implementing quickly, and having access to large panels.

However, due to limitations in the use of these data identified for medical device manufacturers; the place of real-life data in post-market clinical follow-up activities is not always optimized. Among the main weaknesses of these tools we may note:

- i) The compartmentalization within the framework of the health data warehouse and the independence of these approaches, which do not always provide answers to the deficiencies identified in the clinical evaluation files;
- ii) The very restricted and limited access to medical device manufacturers;
- iii) The operating cost of these tools (depending on the methods of accessing the data in each data warehouse), which remains relatively high despite their economic nature;
- iv) The difficulty of exploiting and comparing data processing due to the diversity of data sources, the cross-referencing of structured and unstructured data, and the non-standardization of certain data such as the designation of medical devices (reduced interoperability).

3.3 Prospects of using Real-Life Data in Post-market Clinical Follow-up

In order to consider the prospects of using real-life data warehouses and the future role of these tools in the context of post-marketing clinical follow-up activities, a bibliographic research was conducted. This consisted of identifying, among the technological, organizational and regulatory developments identified in the literature, various avenues for overcoming the limitations of use

previously identified. It should be noted that the possibilities of improvement presented in this section are not intended to be exhaustive.

3.3.1 The Health Data Hub: A Single Platform to Facilitate Access to Data from Various Sources

The Health Data Hub was officially created on a national scale, by the law of July 24, 2019 on the organization and transformation of the healthcare system. Its creation is one of the highlights of the French strategy for artificial intelligence. The Health Data Hub aims to create a dynamic ecosystem for the innovative exploitation of health data. The objective of this project is to facilitate the sharing of and access to health data from a wide variety of sources by creating a unique platform to promote research. This platform must be able to facilitate the reconciliation of health data from various sources (National Health Data System, various real-life data warehouses, registries, cohorts, learned societies with clinical databases including connected objects, health surveys, prevention data, school medicine, occupational medicine, etc.) and their exploitation from a regulatory and technical viewpoint. It must act as a trusted third party between data producers and users and be accompanied by a service offer that includes support procedures, matching operations between datasets, support for data collection and consolidation, and the provision of human and technical resources to exploit them (Villani, 2018; Marc Cuggia, 2019; Chloé Picavez, 2019).

In light of these ambitions, the Health Data Hub should become a true enabler for the use of real-life data by medical device manufacturers.

3.3.2 UDI: Structuration and Standardisation of Medical Device Identification

Following the example of the FDA, which has made the Unique Device Identifier (UDI) mandatory since 2013, Regulation (EU) 2017/745 now requires the implementation of the UDI for all devices governed by European regulations (except for custom-made medical devices and devices under investigation) in order to improve patient safety and optimize their care pathway. The unique identification number for medical devices is an alphanumeric code containing standardized information to identify each medical device placed on the market (with a part related to the identification of the manufacturer and the model of the medical device (identical for all medical devices

with a common designation:UDI-DI) and a variable part related to the production unit of the medical device (UDI-PI)). In order to ensure traceability of medical devices, the unique identification numbers are recorded and stored in a common European database accessible to all member states: EUDAMED (European database on medical devices) (Elisabetta Bianchini, 2019; Dorothée Camus, 2019).

With the standardization of medical device identification, UDI presents a real opportunity for the use of real-life data warehouses by medical device manufacturers.

3.3.3 Digitization of Patient Monitoring for the Benefit of Patient Intervention in Evaluating the Quality of Care

The development of online platforms is booming. They now involve the patient, who must enter information related to his or her quality of life or more specific dimensions such as physical functioning, satisfaction, the relationship with care providers, etc. This evolution is part of the process of continuous improvement of practices. Indeed, it is becoming essential for the patient to participate in the evaluation of the quality of care in real life. By using PROMs (Patient-Reported Outcomes Measures) and PREMs (Patient-Reported Experience Measures), patients can describe their feelings and their experience in real time and in detail and prevent adverse events from occurring (Lisa S. Rotenstein, 2017; Rie Fujisawa, 2018).

The use of these new sources of real-life data is a real opportunity for medical device manufacturers, healthcare professionals and patients. Indeed, the exchange of information should make it possible to improve the manufacturer-practitioner-patient relationship and to adapt the therapeutic strategy in an individualized manner and/or on a global scale.

3.3.4 Portable Devices for Monitoring the Health and Fitness of Subjects

The use of portable medical devices is now an integral part of the monitoring and treatment of certain chronic diseases such as diabetes or certain cardiac pathologies. The use of portable fitness-tracking devices is also becoming more common. For example, consumers are equipping themselves with connected scales or watches in an effort to improve their health and fitness. Wearable devices that include connected bracelets and watches, sensors or any other medical device collect information through consumer and patient declarations and also passively. This passive, automated collection of information from

sensors is done directly with interfaces connected to databases that concentrate information from various sources and of various types (Catherine Dinh-Le, 2019).

The data-processing possibilities offered by the use of portable devices for health and fitness monitoring are numerous. So exploiting these new data sources could become widespread for the evaluation of the performance and safety of medical devices. This is a real opportunity for medical device manufacturers. However, the acceptance of these tools by patients, healthcare professionals and competent authorities; the respect of regulations for data access and exploitation (ethical, legal, etc.); the standardization, processing and development of predictive analysis models for the exploitation of data are still obstacles to the democratization of the use of these tools.

4 CONCLUSION

The entry into force of the new medical device regulations has required manufacturers to review their clinical evaluation processes. Among the major changes brought about by the overhaul of the European medical device regulatory framework are the dimensioning of clinical evaluation, requirements for post-market surveillance and post-market clinical follow-up. Post-market clinical follow-up is now a key activity for manufacturers to keep their medical devices on the market.

Recognized in European regulations for the first time, the collection of real-life data and the use of massive databases are methodologies of interest for post-market clinical follow-up activities. Although the use of these tools has multiple strengths and benefits, the associated weaknesses and limitations do not yet allow medical device manufacturers to fully exploit them. Consequently, material-epidemiology studies and massive databases of real-life data are currently only complementary to other post-market clinical follow-up activities because they rarely meet all the targeted objectives.

In view of the multiplicity of solutions developed or being developed to combine data sources, facilitate access to medical device manufacturers, standardize data and feed data warehouses with new sources of information, the use of real-life data warehouses is expected to soon become a key part of post-market clinical follow-up activities.

In order to better define the future role of these tools in the clinical evaluation of medical devices, an update of the technological and regulatory

surveillance should be considered in order to exhaustively identify developments to facilitate their use. The obstacles to the use of real-life massive databases in post-marketing clinical follow-up activities must also be identified. The ethical aspects (pseudonymized and anonymized data) of massive databases, which are a major topic, should be addressed in this update.

Lastly, this article is based on a purely industrial vision (small to medium-sized companies responsible for the marketing of medical devices). One way of working would be to widen this reflection to a more global vision including the viewpoints of the different actors involved in material-epidemiology studies and the exploitation of real-life data.

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