

Practices and Requirements of Stakeholders Involved in the Clinical Evaluation of Innovative High-risk Medical Devices: A Qualitative Study

Catherine Roussel¹, Alexandrine Salis² and Sylvia Pelayo³

¹INSERM CIC 1415, University Hospital, Tours, France

²INSERM FCRIN UMS 015, University Hospital, Toulouse, France

³Univ. Lille, INSERM, CHU Lille, CIC-IT 1403 - Centre d'Investigation Clinique, EA 2694, F-59000 Lille, France

Keywords: High-risk Medical Device, Risk, Evaluation, CE Marking.

Abstract Medical Devices are health products that combine complex technologies and new organizations. They are under high constraints, both economic and regulatory, but also in terms of quality and safety requirements. The new European regulation comes in addition and questions all of the actors of the maturation process from the idea-to-market for medical devices (MDs). The objective of this qualitative study was to collect and analyze feedback from various European stakeholders involved in the clinical evaluation of medical devices, with a special focus on innovative high-risk medical devices. This paper presents the results of the first phase which scope was limited to France with sixteen interviews. Results show the complexity of the clinical evaluation of MD, particularly when dealing with an innovative, high-risk medical device. The need for training and support of actors through specialized platforms was highlighted, as well as the need for coordination between public and private actors, from the upstream phases of R&D. The collection of clinical data must be part of an overall strategy considering the maturation cycle of the product and its different dimensions. The collection of real-life data must be amplified and structured, with the contribution of new digital technologies opening up new fields of research. This approach must be strengthened by (i) the development of methods based on choices justification, and (ii) making it possible to capitalize on and cross-reference data on the Medical Device throughout its life span. The brief overview provides convergent conclusions, but the understanding of the required level for the evaluation of medical devices and of the way to reach it was not uniform. This reflects a heterogeneous sector and it introduces the need of compromises regarding development strategies and methodological approaches.

1 INTRODUCTION

What complexity when you are interested in medical devices (MDs) and their evaluation! You find a large and heterogeneous field of products with a combination of advanced technologies. These are essential tools in the delivery of innovative medical care, in acute or chronic diseases as well as care of the elderly. The transformational process from the idea to the market requires many actors and experts to go beyond high constraints as performance and safety of the medical device, quality, regulatory, and economic requirements. Scientists, industrialists and regulatory bodies are lead to improve their skills and organizations to be able to develop robust evaluation of their MDs. Thus, they will ensure a better access of European innovations in competitive international

markets. Approaches and methods for MDs development are very specific, particularly with regard to clinical evaluation. Stakeholders of the domain are concerned about the impact of the new European regulation (UE) 2017/745 which now requires to carry out clinical investigations for high-risk devices (current class III medical devices and implantables), this based on a stringent and continuous evaluation plan all along the product lifetime. Regarding the dynamic of the industrial sector mostly containing very small or small companies, these changes have to be supported. In this context, it is interesting to question the level of convergence of the various stakeholders involved in the evaluation of MDs, in terms of practices and needs, especially for the development of innovative high-risk devices.

The purpose of the project was to gather and analyse feedback from European stakeholders involved in the clinical evaluation of innovative, high-risk medical devices: academic researchers, clinicians, promoters, notified bodies, French health authorities, the ANSM (French Agency for the Safety of Health Products), the HAS (the French national Health Authority), the CNEDIMTS (the National Commission for the Evaluation of Medical Devices and Health Technologies) and manufacturers. This work was a first step focused on French stakeholders.

The objectives were:

- to elucidate how the clinical evaluation of medical devices is performed;
- to grasp the key points and success factors in the clinical evaluation of medical devices;
- to evaluate the main obstacles to the development of medical devices;
- to identify the various expectations and recommendations of all those involved.

2 METHOD

An exploratory research method was used to investigate the question, not clearly defined and formalized at the time being, to have a better understanding and overview. The method of survey was chosen to gather information from a predefined group of respondents. A group representing most of the relevant stakeholders in the domain was defined to reach as far as possible data saturation. Semi-structured interviews were performed with the various players in the MD sector over a period of one and a half months, from the end of March to mid-May 2019.

Stakeholders who took part in the study were all involved in the clinical evaluation of innovative medical devices. The sample was chosen to be representative of all those involved in the cycle of innovation, both from the public and private sectors : academic promoters (head of platform, methodologist and project coordinator in a living lab), university hospital pharmacovigilance manager and the head of the medical device committee (Commission for medicinal products and sterile Medical devices- COMEDIMs), University Hospital surgeons (orthopaedic surgery network) and private clinic surgeons, representatives from the medical device industry (CEO, regulatory officer, distributor), SNITEM professional organisation, French authorities in charge of evaluating the ANSM files, HAS files.

All stakeholders were asked to talk about their practices, needs, difficulties and potential suggestions to facilitate the process. The contents of the interviews were processed in a transversal way to pinpoint recurring themes and keywords from the verbatim reports, with two readings performed by 2 independent operators.

Sixteen interviews were performed lasting ~1 hour. Eleven interviews were held over phone and five of them were face-to-face. All the verbatims were transcribed. A content analysis was performed to identify the most recurrent themes. The most significant verbatims were kept to illustrate the purpose and to respect the integrity of the statements without any bias.

3 RESULTS

Feedback from the experiences of the participants particularly emphasized the heterogeneity of the sector and the diversity of existing MDs. Nine topics of interest presented hereafter, transpired from the study: first, the particular aspects to MDs were naturally highlighted. The eight other topics merge in two parts: on the one hand the key points related to the evaluation of MDs, including the risk assessment, and on the other hand the needed strategy for developing MDs. These results are close to already known data, in particular some of which were presented in the General Economic Council reports (Picard, 2017, 2019).

3.1 Particular Aspects of MDs

What came out of this work is that the demonstration of conformance to essential requirements requires to take into consideration many specific aspects to MDs and their evaluation. Indeed, while some aspects are common to the development of a drug or a health product in general (regulatory aspect, extension of the indication, collaborative mode, risk, market...), some others are typical of the evaluation of MDs (e.g. evolutivity, usability, engineering, performance, psycho-social aspect, context of use).

High-risk MDs are all the more concerned by issues such as instrumental, biocompatibility, reprocessing procedures, product lifespan and real-life monitoring aspects.

With this in mind, one of the new requirement imposed by the new European regulation could help: the unique reference number of legacy devices (IUD) which will be used for the registration on a european database named EUDAMED. This new interoperable

EUDAMED will be multipurpose: a registration system, a collaborative system, a notification system, a dissemination system (open to the public). Thus, IUDs could help monitor the device timelife and influence both the evaluation approach and the overall strategy plan.

One of the Success Factors in the Development of a MD is the Consideration of All These Specificities and in All the Various Aspects of the Evaluation, Right from the Early Stages and Throughout the Product Lifetime.

3.2 Evaluation Approach for MDs

3.2.1 Issues with the Instruction of Study Design Files by the Different Competent Authorities

The European regulation (UE) 2017/745 introduced a reinforcement of responsibilities and scope of regulatory authorities. In France, this has significantly modified the studies concerned, the involved actors and the CE marking files evaluation process, which has led to difficulties with regards to the files instruction:

- **Within the Institutional Review Board (IRB):** blockages, longer waiting times, disparity of evaluations, lack of expertise of members of the boards, increase in the volume of studies.
- **Reinforcing the Skills of Notified Bodies (NB) is Also Identified as a Necessity:** the European regulation has a strong impact on the NBs work: difficulties in obtaining or renewing CE marking, blockages, lack and search for competence; the NB's expectations are reinforced with anticipation (right from before 2020); evaluations depending on evaluators; the lack of clarity in regulatory requirements giving way to interpretations, and leading to differing opinions within the teams of evaluators; heterogeneity of expectations for the validation of special processes (sterilisation, cleaning) between Class IIa and III MDs.
 - **Better Linkage between Expectations and the Responses of the Various Regulatory Authorities Has Become Essential:** A lack of clarity in recommendations transpired as well as a lack of coherence or linearity in the evaluations « *a superposition of evaluations* » and the absence of a direct link between evaluations, causing misunderstandings. CE marking evaluation and evaluations for reimbursement purposes correspond to different requirements. The manufacturers need to really know the

requirements of each desk as well as their criteria, in order to coordinate their studies and capitalize the data collected. This requires good coordination in the recommendations in a context of regulatory change.

A strong Expectation for Official Guidelines (Regarding European Regulation) Was Brought to Light, as Well as the Necessary Corresponding Training for All Those Involved to Avoid Evaluator-Dependent Evaluations.

On the other side, authorities have reminded the importance to improve the quality of submitted files with a robust, rigorous and scientific procedure.

One of the Recommendations Was to Carefully Line up the File-building for the CE Marking with the Expectations of the Regulatory Bodies; a Strong Argumentation for the Technical and Methodological Choices May Help the Evaluators When Examining the Files.

3.2.2 Importance of a Multidisciplinary Evaluation Approach

Several points were emphasized by the different stakeholders:

- The importance of integrating a global highly expert multidisciplinary approach in the evaluation of a medical device was especially emphasized by health authorities;
- All of the participants agreed with the need to facilitate connections and interfaces, with accompaniment from platforms or structures, “*specific and reactive places for evaluation*”, to stimulate the clinical investigations and reinforce the cooperation between industrials and academic centers (e.g. <https://www.cic-it.fr/> ; <https://www.forumllsa.org/>).

Formalising the industrial's expectations right from the first contacts by using specific tools as a « Project form » is advised by the platforms managers;

- The difficulty of billing this accompaniment (e.g. in the file-building stages of application to Calls for Projects),
- A reminder that the members of regulatory authorities don't have an advisory role;
- The lack of visibility on existing academic support structures and the lack of gateways.

The Importance of Developing a Multidisciplinary Approach to Get through All the Stages of the MDs Life Cycle Was Elucidated Along with the Contribution by Dedicated Platforms/Structures and Academic Skills.

3.2.3 Recommendations from Competent Health Authorities for Clinical Investigation

Stakeholders from the different health authorities' structures stressed several specific points related to clinical investigation:

- To search for a cutting-edge infrastructure where studies can be conducted, to be able to comply with both logistics and reactivity needs;
- The idea of « right choice » is highlighted for several aspects, i.e. not just regarding the “right” investigators, but also the “right” location of investigations and the “right” methods;
- To justify the procedure, the made choices with a logical approach: « *What question do I have to answer? What would be the appropriate methodology? Why can't the ideal model be applied? How can I break down the model and how can I justify the final methodology I've chosen?* »
- The advisable sources can be found on the HAS website (HAS, 2017, 2019). The methodological guides of the United Kingdom (NICE Guidelines – National Institute for health and Care Excellence) are also quoted as a reference.

The Justification of Choice in Terms of Methodological Approach is Strongly Recommended by People in Charge of Evaluating Regulatory Files. The Choice of the Best Methodology Depending on the Specificities of a MD is Presented as a Key Factor. Thus, Establishing Original Models is One of the Major Challenges for the Domain. With This in Mind, Public/Private Collaborations Appeared to be Essential. The Importance of Being able to Identify the Right Investigators was Emphasized, as Well as Being Able to Find the Supporting Structures. Those Are Essential for the Smooth Running of Studies.

3.2.4 Importance of Users and Usability Studies

The points underlined about usability studies were as follows:

- The importance of taking into account feedback from users in the development of a MD;
- Usability studies which may take place early in the process and all along the development cycle;
- Usability formative evaluations positioned upstream may lead to early feedback;
- In final phases, the absence of new risks may be validated through usability summative evaluation

before CE marking: the figures are well defined, with a clear purpose, the method is clearly identified, i.e. user testing. The medical device's risk level does not seem to have any impact;

- In the design phase, the degree of fidelity of the simulation may be greater or lesser depending on the type of MD, with a high level simulation for high risk medical devices (simulation laboratories, phantom);
- During post-market evaluation, interviews may serve to understand the actual use and feedback on incidents; a decision tree may be formalized to evaluate the interest of going back to a usability evaluation. The risks related to the use of the MD must be re-assessed as the MD evolves. For these real-life studies, the methods are the same but study designs must be provided for depending on the context: town/hospital, public/private sector, etc.
- The interest of developing protocols combining a clinical study with the use of the MD is stressed. However, these methods have not yet been completely successful: « *It's complicated to add an extra secondary objective to a protocol which already holds many questions. The investigation time may still be leveraged to lead to ancillary observations* ».

Usage Studies (User-based Studies) Now Have All Their Importance in the Evaluation of Technological Innovations and May Be Used and Adapted throughout the Lifecycle of MDs. In a Context Dictated by Organizational, Time and Budgetary Restrictions, it Has Become Interesting to Develop Methodological Approaches Combining Both Clinical and Usage Aspects.

3.2.5 Role of the MDs Risk Level

Finally, one of the purposes of this work was to identify the role of the risk level of the MD in the strategy and the evaluation methods:

- The notion of risk appeared as a rather relative datum: « *Rather talk about MDs subjected to mandatory clinical investigation; not forgetting everything that's non-implantable (quality defects, raw materials); there is no “small” DM* ».
- The evaluation methods were not presented differently by the participants according to the MD Class. The essential requirements are similar whatever the Class, just the level of requirements is higher with a mandatory clinical investigation for implantable and Class III MDs (except in cases

wherein resorting to existing clinical data may be rightly justified).

- The HAS report on the elaboration of guidelines on the methodological specificities of clinical evaluation for MDs indicates that « *the methods for evaluating connected medical devices are identical to those of other devices... the complexity of evaluating a connected medical device has been emphasized due to its organisational impact and its impact on the patients* ». The CNEDiMTS files evaluated in this report concern many implantable connected medical devices.
- The ANSM's « Degree of originality » form relative to medical devices proposes several degrees of originality (from minor to major innovation), depending on the level of technological breakthrough and clinical impact. Perhaps this type of segmentation could act as a better guide for new methodological recommendations than categories of risk?

It Was Revealed That a MD Should Be Analysed as a Whole, beyond Merely Identifying the Risk Category. « *The clinical investigation is mandatory for implantable and Class III medical devices, and its absence remains the exception* ».

3.3 Overall Strategy for MDs Development

3.3.1 Critical Points for the Small Companies and Start-ups of the MDs Domain

Several points were highlighted as critical for small companies or start-up:

- The importance of having a strategic vision right from the design stage and defining the position of the MD in the therapeutic arsenal early on.
- The importance of involving experts in the field (health professionals, key opinion leaders) right from the early stages to match the requirements of industrials with the expectations of clinicians and establish the development plan. The manufacturer's participants emphasized the difficulties in identifying and approaching clinical experts. Most of the participants agreed on the fact that public platforms/structures could facilitate this contact.
- The importance of working out the business plan very early on (target: French, European or other market) in order to anticipate the procedures and studies to be carried out; plan the economic model from the outset depending on the claims, potential

sources of funding, and envisage public/private collaborations to benefit from national or European public funding. The HAS (French national Health Authority) innovation grant provides co-funding for clinical studies on highly innovative medical devices by the public authorities. « *The sense of anticipation is a key-factor for DMs development* ».

- Work is currently being carried out to establish centralised procedures on a European level: EUnetHTA network (European Network for Health Technology Assessment), and INAHTA (International Network of Agencies for Health Technology Assessment), and early meetings are being set up.

To Manufacturers, We Give the Following Advices: Anticipate Their Overall Strategy, Validate Their Clinical Claims with Experts from the Field and Anticipate Their Economic Model.

3.3.2 Access to the Market and Marketing

It is recommended that manufacturers anticipate the reimbursement request process: in France, the National Commission for the Evaluation of Medical Devices and Health Technologies (CNEDiMTS) gives notice based on criteria defined in the regulations. The interviews did not highlight any evidence of criteria specific to high risk MDs. The requirement level appears to be appropriate to the clinical context; hence there are more requirements for high-risk and implantable medical devices.

The Functioning of the Public Sector Was Pointed Out: hospital procurement procedures are subject to government rules; the purchasing process at the hospital is highly complex and lacks visibility for industrialists.

The indexing of innovative devices in public health facilities appeared to be structured:

- In short, knowledge about the requirements for this evaluation may help to guide the right choices regarding criteria to be evaluated upstream, and what methods should be used to achieve it.
- Constituting a multidisciplinary indexing committee proved to be pertinent for evaluating and validating the purchase of a medical device: evaluation of the interest of the medical device relative to the existing therapeutic arsenal, evaluation of practices, requirements, contribution to safety and the level of safety, intended use, cost (link with the Estimated Revenues and Expenditures). Clinical studies as well as publications are involved in the decision-

making. A lack of comparative studies versus the gold-standard device and links between studies was revealed; knowledge of the medical device as a whole remains a real difficulty for end-users (product lifespan, conditions of re-use, means of sterilization, evolution of the medical device...).

- Analyse of various pertinent criteria for evaluating the quality of the product (the medical device itself and its packaging) relative to the medical device retained as a reference, with a weighting system; the medical advice must overtake the economical interest only. An official regulatory decision tree is also interesting for material vigilance decisions.

A Comparison with Operations in the Private Sector Appeared to Be Interesting:

- Absence of a tender process or an indexing system is a difficulty for practitioners; the choice of medical device seems to be made depending on available stock, and the sales force.
- Superiority studies and available post-market data are also insufficient with respect to the ever-changing nature of surgical equipment.

Material Vigilance Monitoring and Post-market Studies Were Another Point for Attention:

- For Class III and implantable medical devices the monitoring plan (PMS = Performance Monitoring System) is updated at least once a year.
- The particular example of implantable prostheses was studied: the basic specifications must be developed, specifying « *how many prostheses, at how many years, with what follow-up, what grid should we use to evaluate the product* The guidance of the National Institute for Health and Care Excellence (NICE) are still precise ; in France, it depends on the experts ».
- Favouring studies in which the University Hospital is the promotor of the study would allow the manufacturer to guarantee independence of data, and favour the publication of negative results.
- The extent of post-market follow-up (type of study, duration of follow-up) is confronted with the principle of reality. It comes down to finding the right compromise in order to remain within a reasonable price-range.

The Conclusions Retained are That Manufacturers Must Present a Clear Process Regarding Their Claims, to Construct an Appropriate Clinical Development Plan, so That it is Possible to Obtain Data on the Clinical Benefits

and Position of the Medical Device in the Therapeutic Strategy.

3.3.3 Need of Accompaniment and Training of Stakeholders

- Scientific approaches and methods used to demonstrate the efficacy of a MD in the current files have their limits;
- There is a real need for learning, teaching and accompanying in the construction of a development plan and at each stage of development;
- The lack of a global vision and knowledge about the various stages in the progress of MDs, the lack of information and referencing of the players to solicit is presented as difficulty.
- The official guides, supports, summary documents are difficult to identify.

Awareness of the New Regulation, Training and Accompaniment of Those Involved Has Become a Challenge for the Development of Medical Devices.

4 DISCUSSION

The analysis of all the feedbacks from experiences showed the complexity of the clinical evaluation of MDs, particularly when dealing with an innovative, high-risk MD, “*manufacturers have to develop cutting-edge expertise or deep analysis in very diverse fields*”. Regarding this, emphasis should be placed on: make the industrials aware of the problem, strengthen training and developing accompaniment via specialised platforms, as well as favour interactions between all those people involved in the evaluation. “*The innovative start-ups succeed if gathering a set of technical regulatory and clinical skills*”. However, “*there is a lack of skills, gateways, advices and organizations*”.

The gathering of clinical data must be reinforced and anticipated in accordance with the overall strategy, with the establishment of new adaptive methodologies responding to the specific requirements of a medical device evaluation. This should open a wide range of opportunities to adapt existing models or create new ones. Real-life data collection must be amplified and structured with the contribution of new digital technologies (big data), opening new fields of research.

The overall strategy of manufacturer must be anticipated and this should draw on a methodological procedure based on justifying choices according to

clinical and therapeutic benefits and the interest of the various available options and economic models for public health. Lastly, as part of the reinforcement of regulatory requirements, regulatory bodies must gain coherence and homogeneity. It is important to issue official recommendations. Linkage and structuration of the players in the sector must be continued, taking into account all needs in terms of resources (human resources and expertise) to find the right balance and continue to innovate.

Within the group of MDs, high-risk devices may pose a greater risk to patients. Several European organisms stress the importance to shape, within the limits of the European legal framework, a coherent set of rules, procedures, referentials for a guided, responsible and reasoned maturation process of this specific kind of MDs (Neyt et al., 2017). This work is a first step with the gathering of feedbacks from most of the French stakeholders involved in the process. The work will be continued by a collection of data at a more European level as part of a European project to support and guide stakeholders considering bottlenecks and strenghts of all the European countries.

Some biases of the study have been identified. The biases related to the sample are:

- The profiles of certain protagonists who had more experience of Class I MDs rather than high-risk MDs;
- The absence of inclusion of some important perspectives in the interview panel such as the end-users (e.g. patients, healthcare professionals), specialized scientific societies, Notified bodies and the Commission for the evaluation (CNEDiMTS).

The biases related to the method are:

- The possible lack of thorough questions about the methods in the cases of high-risk MDs;
- The study was performed over a short period and in a highly evolving context. The issues identified must be regularly put into perspective;
- These results will have to be completed by a « quantitative » investigation via a new questionnaire focused on innovative high-risk MDs;
- Three themes deserve to be addressed to complete the study: first, the ethical vision (questions about the risk-benefits ratio, acceptance of the technology or dependence on it, the choice and appropriation by the patient or the medical profession); second, the difficult question of conflicts of interest among experts; and third, the unavoidable aspects of intellectual property which must be mastered right from the beginning.

5 CONCLUSION

This qualitative survey provides a current field overview of some actors at French national level regarding the clinical evaluation of MDs. There is a growing awareness of the need to harmonize actions around the evaluation of DMs.

Through the different points of view and the topics addressed, the comments converged to express the interest of a global evaluation strategy of the MD and a methodological approach taking into account the entire maturation cycle and the specific dimensions of each DM, in particular for high risk MDs. However, this approach must be strengthened by the development of methods to capitalize and combine DM data throughout its life cycle. A better coordination between public and private actors, starting from the upstream phases of R&D, will help researchers, developers, academics, industrials, pharmacists, hospitals professionals, to conduct first a prototype to a CE marked product and then a CE marked product to a reimbursed product.

REFERENCES

- Haute Autorité de Santé (2019). *Spécificités méthodologiques d'évaluation clinique d'un dispositif médical connecté (DMC) : Rapport d'élaboration du guide sur ses spécificités d'évaluation clinique, en vue de son accès au remboursement*. Retrieved from https://www.has-sante.fr/portail/upload/docs/application/pdf/2019-02/rapport_methodologiques_devaluati_on_clinique_dun_dmc.pdf
- Haute Autorité de Santé (2019). *Guide sur les specificites devaluation clinique dun dmc en vue de son acces au remboursement*. Retrieved from https://www.has-sante.fr/portail/upload/docs/application/pdf/2019-02/guide_sur_les_spe_cificites_devaluation_clinique_dun_dmc_en_vue_de_s_on_acces_au_remboursement.pdf
- Haute Autorité de Santé (2019). *Principes d'évaluation de la CNEDiMTS relatifs aux dispositifs médicaux à usage individuel en vue de leur accès au remboursement*. Retrieved from https://www.has-sante.fr/portail/upload/docs/application/pdf/2017-11/principes_devaluation_de_la_cnedimts-v4-161117.pdf
- Haute Autorité de Santé (2017). *Parcours du Dispositif Médical en France : Guide pratique*. Retrieved from https://www.has-sante.fr/portail/upload/docs/application/pdf/2009-12/guide_pratique_dm.pdf
- Moreau-Gaudry, A., Pazart, L. (2010). Développement d'une innovation technologique en santé : le cycle CREPS, Concept-Recherche-Essais-Produit-Soins. Innovation and Research in BioMedical engineering, 31, 12-21.

- Neyt, M., Baeyens, H., Pouppez, C., Slegers, P., Hulstaert, F., Stordeur, S., Vinck, I. Introduction of high-risk medical devices: national measures that can be taken under the current European legislation to put the patient interest central. *Expert Review of Medical Devices*14:3, 181-188.
- Picard, R., Renaud-Mazataud, N. (2017). *Attractivité de la France pour les entreprises de santé*. (Rapport N°2017/06/CGE/SG). Conseil Général de l'Economie.
- Picard, R., Fagon, J.-Y., Diebolt, V., Oget-Gendre, C. (2019). *Réflexions stratégiques sur la politique industrielle en matière de dispositifs médicaux*. (Rapport N°2018/26/CGE/SG). Conseil Général de l'Economie.

