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The New European Medical Device Regulation: Place of Surgeons in the Clinical Evaluation

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Abstract: The new European medical devices regulations now require manufacturers to evaluate the devices used by surgeons over the long term, which is necessary both to support CE marking and marketing applications and to monitor their performance and safety. The adherence of the Health Care Professionals (HCP) to the clinical evaluation and to the studies is essential to deliver quality data, which supports the files of CE marking, and ultimately contributes to the innovation of health technologies.

Keywords: Medical Devices Regulation • Clinical Evaluation • Applications • Ethical Issue • Surgeons

Abbreviations: CE: Conformité Européenne; HCP: Health Care Professionals; RCTs: Randomized Controlled Trials; NB: Notified Body

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INTRODUCTION

Physicians in general are the main users of medical devices when they use them with their patients, and according to the indication of the device and the instructions provided by manufacturers. With the European regulation, the evaluation of medical devices of any class is necessary to demonstrate and monitor the risk-benefit ratio, both in their development and throughout their life cycle. It is then that the surgeon asked to evaluate these products in clinical trials that are intended to be rigorous and meet regulatory requirements.

NEW EUROPEAN MEDICAL DEVICE REGULATION

The application of the new European regulations is a major adaptation challenge for companies and for health systems in Europe. The European regulations governing the marketing of medical devices have been constantly evolving since their implementation in 1998.

These health products, whether they are reimbursed or not, must be subject, prior to their marketing, to an assessment with regards to safety and performance requirements, including in particular the demonstration of a favorable benefit/risk ratio.

A notified body verifies this assessment (NB), during a specific CE marking certification process (medical CE marking), the terms of which are all the more restrictive as the risk class of the medical device is high. A total overhaul of this regulation has been in place since May 26, 2021, through the application of the new European regulation 2017/745 amended by regulation 2020/561.5 [1].

The clinical evaluation introduces the notion of identifying the degree of novelty of the device according to the degree of novelty sheet of a medical device (Table 1).

Table 1: Sheet of degrees of novelty of a medical device from the French Drug Agency ANSM.

Degree of novelty	Type of novelty	Innovation where the dominant is		
		Technological		Clinical
5	Major innovation	Breaking technology	And	Strong clinical impact
4	Innovation (Innovative device)	Breaking technology	Or	Strong clinical impact
3	Substantial novelty	Incremental technology	And	Moderate clinical impact
2	Moderate novelty	Incremental technology	Or	Moderate clinical impact
1	Lacking or minor novelty	Known technology	And	Unchanged clinical impact

This regulation considerably reinforces the prerequisites are necessary to obtain medical CE marking as well as the traceability and transparency tools. It increases the requirements concerning the level of demonstration of the benefit/risk ratio, in particular on the expectations in terms of pre-marketing clinical evaluation and post-marketing clinical evaluation, throughout the life of the medical device. Its application is a major adaptation challenge for both companies and European health systems.

The list of safety and performance requirements has been clarified and extended in Regulation 2017/745. The first of the requirements aims for a favorable benefit/risk ratio of the medical device considered in its indication and its conditions of use. The possible risks associated with the use of the medical device must remain acceptable about the clinical benefits provided to the patient. The manufacturer must in particular take into account the state of the art and the level of knowledge and skill of the user (who may be the lay patient or a healthcare professional) in order to implement risk control measures.

Demonstration of the benefit/risk ratio is essentially based on two major documents in the technical file of a medical device:

1. The clinical evaluation report.

2. The risk management report.

This report is continuously reassessed by the manufacturer and checked by the notified body, with regards to the data collected as part of post-market surveillance and vigilance. Beyond this basic requirement, the other requirements are numerous and cover design, manufacture (including data relating to the lifetime of the device), the information provided with the device, etc. Demonstration of compliance with a general safety and performance requirement must be based on existing reference systems and in particular, harmonized European standards.

Manufacturers are required to put in place a post-marketing surveillance system enabling them to proactively collect relevant data on the quality, clinical performance, and safety of a device throughout its lifetime, in order to define and apply any preventive or corrective measures and to ensure their follow-up. They must also put in place a reactive process for dealing with serious incidents involving medical devices (Materiovigilance) in order, in particular, to report them immediately to the competent authorities and to carry out corrective actions to prevent the occurrence of the same type of incident again. During the period of validity of the certificate issued by the notified body, the latter verifies by annual, systematic, on-site audits, that the regulatory requirements continue to be met and that the post-marketing surveillance procedures (including the vigilance) put in place by the manufacturer are effective. The notified body also schedules additional or unannounced audits to monitor specific situations for the implementation of corrective actions. For the renewal of the certificates, as well as in the event of substantial modification of the device, the notified body carries out an in-depth check of the technical documentation and the quality management system. The requirement for demonstration of clinical evaluation has always existed in European regulations and its methods have regularly changed, in particular with the publication of the major amendment to the directive in 2007 (directive 2007/47/EC) and in the different versions of the guide of the European Commission for the application of the directive dedicated to clinical evaluation (MEDDEV 2.7.1). Regulation 2017/745 further strengthens the requirements for demonstrating clinical evaluation. The principles apply to all medical devices, regardless of their class, and are based on a combined analysis of the literature and clinical investigations specific to the medical device concerned, taking into consideration therapeutic alternatives. For implantable devices and class III devices, it is necessary to conduct clinical investigations specific to the medical

device in question. The ability to use the demonstration of equivalence, allowing the use of clinical data from the literature on a competing medical device, has been largely restricted in the regulations, making its use very hypothetical. To demonstrate equivalence, manufacturers must now agree to a contract giving access to all product data from the designer manufacturer to its competitor so that the latter can rely on the clinical data of the initial device. In addition, Regulation 2017/745 specifies the need to plan and implement post-marketing clinical follow-up. Finally, the regulation sets up an enhanced clinical evaluation procedure called "Scrutiny" (Article 54), which is added to the traditional certification procedure required and carried out by the notified bodies. It provides, for class III implantable medical devices and certain active class IIb medical devices, the consultation of a panel of European experts. This group of experts appointed by the European Commission gives a scientific opinion on the clinical evaluation report drawn up by the notified body based on clinical evidence provided by the manufacturer and thus allows double verification.

NEED FOR CLINICAL STUDIES

The role of the surgeon in the clinical evaluation of medical devices has become fundamental. It is solicited in the different stages of the clinical investigation. When the manufacturer decides on the go of the study, as the sponsor of the study, he launches a feasibility study to first offer the study to pre-selected surgeons and see with them whether they have the potential for patients to be included in the study concerned and especially if they meet the conditions to conduct a study of good clinical practice. In all cases, the selected surgeons will receive a study of good clinical practice. The major problem encountered with HCP in general when setting up clinical studies is that they are reluctant to conduct these studies, citing various reasons, including lack of time and/or the administrative tasks to follow.

The studies carried out in this context are either clinical investigations whose objective is to clinically demonstrate the efficacy and safety of the medical device and to support the CE marking registration file or are post-market studies of devices already on the market which are then investigations of an observational nature and which measure the impact of these medical devices in terms of their performance and their safety over time since manufacturers demand a lifespan for their product.

There are various studies on the adherence of HCP in general to clinical research.

An epidemiological survey was conducted among general practitioners in France to explore the reasons for their participation in a study. It involved carrying out six semi-structured interviews by two sociologists. 216 questionnaires were sent out, 80 of which were completed and analyzed, and then 18 telephone interviews, which were completed with the information, collected [2-9].

The results gathered the following information. Reasons for taking part in the studies:

- Perceived scientific interest
- Relevance to public health
- The feeling of being a research partner
- Barriers to participation in studies: Blurred image of the sponsor
- Ignorance of the objectives of the survey
- Absence of direct contacts for the communication of information
- Amalgam made between filling in survey questionnaires and administrative constraints in general

From this study, it emerged that better communication, a partnership between research and medical practitioner, the usefulness of the findings of epidemiological surveys for medical practice, and clarification of the role of the promoter were necessary.

An epidemiological study conducted in Japan among 602 doctors with questionnaires sent to doctors from 31 departments of Kyoto University Hospital from October to November 2007 showed the following facts (Table 3) [10]:

Table 2: Declaration of participation in the various types of studies [2].

Participate	Often	Occasionally	Total
Clinical trial	4%	4%	8%
Trial + Pharma's trial	3%	4%	6%
Trial + Pharma's trial + Epidemiologic trial	18%	11%	28%
Trial + Epidemiologic trial	5%	5%	10%
Pharma's trial	3%	18%	20%
Pharma's trial + Epidemiologic trial	1%	16%	18%
Total	**33%**	**58%**	**90%**

- 16% had not received training in clinical research
- More than 50% had already written a protocol or published
- 47% derive a better appreciation of pathologies
- 28% gain a greater scientific reputation
- 2% derive more financial means
- 37% lack of statistical knowledge
- 26% too heavy formalities (administration, eCRF

Table 3: Effect of status, age range, and attitudes to current participation in clinical research [10].

Characteristic	Odds ratio (95% CI)	p-value (p < 0.05)
Past participation in clinical research		
Yes	5.680(2.40-13.441)	< 0.0001
No	Reference	
Prospective participation in clinical research		
Yes	5.756(2.508-13.212)	< 0.0001
No	Reference	
Previous training course in clinical research		
Yes	2.081(0.678-6.389)	0.200
No	Reference	

An audit conducted in India on 19 clinical studies (2014-2018) provides the following information [11-12]:

- 55% of clinical studies are stopped for lack of participants
- 80% of global clinical studies fail to recruit within the time required by the protocol
- 50% to 80% of eligible patients are not recruited by decision of the PdS
- Root cause: PoS did not include, lack of buy-in

It is obvious that doctors in general practicing in academia are dependent on their ability to publish work in international scientific journals to progress in their careers, and therefore to conduct clinical studies. The consequences in terms of scientific, individual, and institutional recognition are major.

An epidemiological survey was conducted in Baltimore in the United States among 30 clinicians and staff members (Table 4). Half of the respondents had experience in clinical trials and the other half did not [13-14]. Participants were asked about motivations and barriers to practice-oriented research in the context of a clinical trial. It emerged that:

- 47% intellectual stimulation: out of their comfort zone
- 40% Improve patient care: publication of results but also all upstream work, literature review, learning, and discussions with patients
- 27% financial benefit (1 HCP/4)
- The published results influence the decision of an HCP to adopt a new MD

A survey by Sumi et al of doctors showed that among those who were studying [3]:

- 47% had a better knowledge of pathologies
- 28% saw an improvement in their position with their colleagues
- 13% received subsidies
- 2% had no interest

Of those who were not studying:

- 37% lacked statistical knowledge
- 26% considered the formalities too cumbersome (administration, eCRF)

These data extracted from different surveys show that

Table 4: Reasons to participate in pragmatic clinical trials as offered by experienced vs. non-experienced clinicians and staff members [13].

Reasons cited	Experiences (15 informants)	Not-experienced (15 informants)
Benefits oriented to patient care Offer free medicine/care	2	0
Offer care they need always as part of study	2	1
Affords more care time with patients who want it	1	0
Early access to new treatments	3	0
Create knowledge for patient problems	6	3

Solutions to difficult patient problems	2	1
Real-world patients in clinical trials	1	2
Get patients involved in own care	1	2
Quality improvement	0	1
Benefits not oriented to patient care Gain competitive edge in practice	4	1
Financial benefits	4	2
Intellectual stimulation in practice	7	1
Knowledge for benefit of society or community	6	1
Professional development	5	1
Total reasons cited	**45**	**16**

collaboration between private or public health professionals, surgeons, and industrial promoter is fundamental to develop innovation, data quality, and the registration of new devices and treatments [15].

DISCUSSION

The healthcare professional and the surgeon, in particular in studies concerning the evaluation of their devices, remains a very important partner in the logistics of clinical studies. For the proper implementation and monitoring of these studies, he must adhere to them upstream. Define common objectives with the stakeholders, collect the data, avoid queries to optimize the time on site of the monitors, master the electronic tools of collection of data and other study tools, and finally knowing how to transform regulatory requirements into valorization for innovation and new treatments intended for patients. Clinical studies in surgery remain difficult to set up from a methodological and ethical point of view.

In surgery, the application of the concept of evidence-based medicine involves specific difficulties. The difficulties are linked to the rarity and relative poor methodological quality of randomized trials and meta-analyses in surgery, to the difficulties that surgeons have in critically analyzing the literature and applying the results provided by the trials to a given patient, and to make surgeons more inclined to apply the principles of evidence-based medicine. However, all these difficulties can be overcome theoretically so that evidence-based surgery is not an ephemeral mode but a definitively established paradigm.

In the studies on the medical device, there is the interventional option, which is put in place when the equivalence is not possible. This will involve setting up a randomized study design and comparing the non-marketed medical device to the standard treatment comparator device.

Randomization can be somewhat difficult to implement. In short, the difficulties encountered in carrying out RCTs in surgery may be related to: on the one hand the feasibility of randomization (ethical problems, the context of emergency, palliative care), on the other hand, the curve of apprenticeship of surgeons, the standardization of operating procedures, the problem of the evaluation of surgical performance, and finally the surgeon-patient relationship [16].

Even if the new European regulation on medical devices has made the evaluation of medical devices even more complex and demanding, it is the quality and safety of health products that have been strengthened for the good of individuals, who are increasingly demanding good care and health professionals always on the lookout for new technologies. These are also the repercussions at the level of the training of health professionals, in particular at the level of clinical evaluation as a whole, but especially at the level of the methodology of trials, biostatistics, and adherence to good clinical practices.

CONCLUSION

The health professional in general remains a major element in the clinical evaluation and the studies required by the new European regulation. It's training in good clinical practices and its adherence can only promote reliable quality data to support the marketing of new technologies that benefit patients.

STATEMENT OF THE PROBLEM

Clinical trials can only be carried out with surgeons who are motivated and well-trained in good clinical practice.

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