End-user Need based Creation of a Medical Device: An Experience of Co-design to Struggle Pathological Scars

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Abstract: Scar is a common visible mark of human tissue healing. Sometimes pathological phenomena lead to abnormal hypertrophic or keloid scars, with evolutions varying depending on different conditions: origin of the tissue barrier disruption, concerned body area, or ethnic origin. Based on these statements, care procedures have been developed to avoid aesthetical or functional impairments: drugs injection, surgery, cryotherapy or mechanical compression. The story will relate the matching of a multi-disciplinary team that focused on covering an unmet need for ear lobe keloid treatment, providing patients an optimal and holistic care. The benefits researched lied in improving the understanding of the disorder, avoiding the recidivism of the scars, diminishing the frequency and duration of care, and in end improving patients' quality of life. The paper will not only narrate the building of a health innovation, on technological, clinical, user points of view, but will also try to detail the evaluations planned at the different stages of development, as well as the challenges, conditions and prerequisites allowing to produce concrete solution.

1 INTRODUCTION: THE MEDICAL PROBLEM

The keloid scar is defined as a pathology of tissue healing resulting from a proliferation of fibrous tissues that extend beyond the limits of the initial wound (Butler et al., 2008). This pathology, described as "pseudo-cancerous", does not put the patient's vital prognosis into threat, but could constitute a severe aesthetic disturbance in addition to inducing serious functional problems, pain and itching, seriously impacting the quality of life of the patients, especially for scars on visible areas of the skin. Available epidemiological data indicate an incidence that can be very high (16%) in subjects with ethnic skin (Bayat et al., 2003).

The management of this pathology by the surgeons is difficult and seems randomly addressed. Indeed, different treatments are proposed, ranging from the injection of corticosteroids, to cryotherapy and the administration of anticancer molecules (Ud-Din et al., 2013). At present, no treatment, or combination of treatments, have been described as effective. The main classical management remaining intra keloid resection, it too often leads to a more serious recurrence of keloid in 45 to 100% of cases (Andrews et al., 2016).

The lack of standard and effective treatment is mainly due to the poor understanding of the cellular and tissue mechanisms involved in the appearance and evolution of keloids. For many years homemade compression techniques have been described in the literature to prevent recurrence of keloids after surgery. Especially the handiworks were dedicated to the ear, area of frequent occurrence of this type of

pathology, often developed after piercing (Brent et al., 1978, Vachiramon et al., 2004, Chang et al., 2005, Yigit et al. Coll., 2009; Park and Chang, 2013; Tanaydin et al., 2016). The effectiveness of these means of compression relies on the reduction of the post-surgical relapse of the earlobe keloid, observed to a range of 10 to 30% (Vachiramon et al., 2004, Park and Chang, 2013, Tanaydin et al. 2016).

Even if these works have been presented, there is no current consensus or shared "gold standard" practice for the treatment of the ear, particularly its compression lobe. One of the causes being the lack of solid clinical trials on the subject (Louis and Gracia, 2010). We proposed then a work assembling from the beginning different experts around the development of a quite unpretentious medical device, which materialize in fact the center of complex considerations.

2 THE ADVENTURE OF EMERGENCE OF THE IDEA

In 2014, a surgeon from our university hospital, contacted the clinical investigation research center for a need related to his clinical practice, in fact the medical problem announced in part 1 of this abstract. His difficulty concerned then the reccurrences of keloid scars on an important proportion of his patients, which he yet treated consciensioulsy with intralesional resection plus corticosteroids - triamcinolone acetonide injection.

Meeting the research engineers, he explained his needs in a system to add to the current care, relatively to the litterature arguments in favor of a compression of these specific tissues on one point, and to the existing proposed solutions on another point.

At the beginning the deal seemed to be fairly simple:
the possibility of adjustment of the pressure by the patient himself (within a limit of the maximum number of magnets imposed by the clinician) would favorize the observance of the device and its comfort. For the few existing studies on the subject, correlation between keloid recurrence of the ear and discomfort in wearing a device has been proved to be correlated (Tanaydin et al, 2016), which may be related to poor adherence to the application of pressure procedure.

Following works in collaborations with other clinicians (to confort the shared property of the expressed need), engineering and business local schools (bibliographic, research & development, clinical, and market analysis successive training periods), as well as with engineering research center, permitted to formalize a state of the art, and the first drafts of the value analysis and specifications of the innovation, in terms of ergonomy, adaptability, cost, aesthetic...

The collaborations led then to the design of a product as well as evaluations all along the progression.

3 TECHNOLOGICAL DEVELOPMENTS: THE "SCAR WARS" PROJECT

Based on brainstorming and on the kind of "Santa letter-writing" desires from the clinicians, but also from the specific anatomical area, and from the technical constraints, the prototypes were first computer-aided designed (Figure 1 left) to format, modelize the idea and project the skateholders into a first view of the possible object.

From that, discussions led - beginning of 2015 - to adaptations before an agreement on the general shape and on primary dimensioning options.

The next step consisted in a 3D printing thanks to stereolithography: few samples of different sizes where produces, manipulated and confronted to the ear lobes of healthy volunteers (from the team…Figure 1 right).

It permitted to define then the size, but also to determine the fact that our idea would need to be constitued of a clip on which magnets could be easily inserted. We had our proof of concept definition prototype.

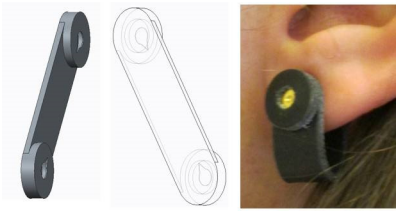

Figure 1: Digital and first physical version of the clip.

At the same time, bench lab tests on magnets figured out their sizing - and in fact the possible applied strengths.

A support associated with a dynamometer system measured the forces in work with different magnets and depending of the distance between.

According to the results, for a coherent lobe thickness plus a pressure to be applied (from the litterature) of 25 to 35 mmHg, we defined that we

would need 2 to 8 neodymium-iron-bore magnets with nickel coating magnets (1mm thickness, diameter 12mm) to be placed on ear lobe.

We needed then to securize the product before thinking of a first use in human. The contact with an industry allowed to produce a mold from which the first clips made with flexible medical grade silicone were manufactured on February 2016 (Figure 2).

In terms of idea protection, an anteriority mark tool was used in December 2016.

It was then the time to think about testing it on targetted concerned patients with keloid scars.

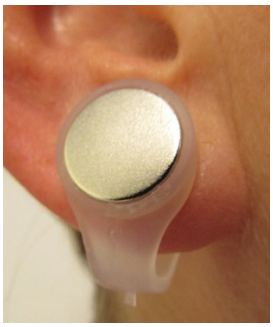

Figure 2: The Scar Wars clip.

4 THE REAL LIFE TEST

4.1 Requirements

In order to provide a product that could be tested during a clinical trial, the responsible manufacturer need to follow regulatory requirements, centralized by the european Medical Device Regulation MDR 2017/745 (repealing Council Directive 93/42/EEC).

Our ambition was to test a product which was not yet CE marked. As a reminder, the CE mark is obtain by a procedure in which notified bodies examine the conformity of the product. On this particular situation (without yet industrial part identified as a owner), our hospital assumed the responsibility as a regulatory manufacturer, for the clinical trial. Actually to obtain the authority agreement to perform the clinical study, we had to provide a file quite similar to the one that would be presented for CE mark obtention.

Thus the team formalize a technical file, including conception plans, laboratory tests, risk analysis, essential requirements answers (list of all applicable standards and the way we addressed it), user manual, labelling and packaging.

This technical file (or “investigator brochure” on a clinical trial language) aim to present the product that will be tested and the security measures taken by the manufacturer to ensure its safety use.

The medical device under study was then defined as related to a Class I according to the requirements of the EC Directive.

On another side, the clinical trial running (or “design”) needed to be described in study documents, the master ones being the study protocol, the informed consent and case report forms. A specific budget had also been searched and obtained to finance the clinical project (hospital internal research call).

4.2 Design of the Clinical Trial

The building of the study protocol was an important phase of our project, and its writing needed to mobilize all the partners. It helped to define the objectives, the criteria of evaluations, the targetted population (characteristics and number), the progress in terms of duration… all this taking into account the data already availables (in the litterature and thanks to our previous advances), as well as the previous realized tests and obtained results.

The main objective was defined as the evaluation of the effectiveness and safety of the compressive device; the main endpoint being then the reccurence (yes/no) of the pathology. The study concerned 27 male and female patients (more than 18 years old) presenting keloid lobe ear scars that needed to be treated by reconstructive surgery; it excluded patients with known allergy to nickel (even if the magnets are not in direct contact, silicone clip making the interface).

After usual management of the keloid scar of the ear (reconstructive surgery and injection of corticosteroids - triamcinolone acetonide), the concerned patients had to wear the compressive device and to adjust the compression with the magnets provided. By consulting the literature, which proposes that the patient wears his compression device 8 to 24 hours a day (Louis and Garcia, 2010), it was decided to recommend to the patient to apply a compression allowing him to wear the device at least 12 hours a day, daily and throughout the duration of study, ie one year. The compression must be sufficient, without being painful. The clinician will rely on these data, individually for each patient, to dictate the maximum number of magnets to be used based on the measured thickness of the patient's ear.

The clinician may reduce the frequency of use of the device, or even stop it according to the evaluation of the quality of healing during visits.

The patients were planned to be seen at 3, 6 and 12 months after intervention, in the traditionnal course of visits during the usual care (no modification due to the trial).

The secondary objectives of the Scar Wars trial focused on a multimodal and interdisciplinary assessment of scar tissues by (Chambert et al., 2019):

- evaluation of patient acceptance and satisfaction, evaluation by the surgeon (specific scars evaluation scales, Draaijers et al., 2004, Deslauriers et al., 2009),
- biometric characterization of the area of interest,
- non-invasive imaging assessment of tissue evolution,
- analysis of the bacterial flora present at the level of the keloid scar,
- the creation of a keloid cell bank, basis of a biological ancillar study allowing our biologists to focus on pathological healing process and anti-fibrotic drug evaluation.

4.3 Official Agreements

The "pilot study evaluating the effectiveness and safety of a compressive device intended to prevent recurrence of keloid scars after surgical resection" file was submitted on February 2017 onto French authorities, with a final positive agreement by ethical committee and national agency for health products – ANSM Agence nationale de sécurité du médicament et des produits de santé – obtained in August 2017.

The trial was recorded on official web platform ClinicalTrials.gov, and the first patient was included in October 2017.

To date, 10 patients have been included, without presenting a reccurence.

5 NEXT STEPS

The enrolment of the last patients and results of the study will feed the CE mark file, which is then already initiated.

Apart for the CE mark class I obtention, the next important stage will be to build the business model and development associated to an official regulatory manufacturer that will handle the responsibilities and assure the distribution.

Concerning the material, the perspectives could lie on the development of different sizes of the clip and magnets, in order to fit as much as possible to different morphologies, or even other area on ear or even face. 3D printing technologies offer also prefigure tailor-made medical devices.

Functionalization with specific drugs or molecules could be the future of such innovations.

In projection, next evaluations could focus for sure on safety aspects once devices will be on the market and largely diffused (material vigilance), and on aggregation and reinforcement of clinical evidences of the innovation. Medico-economics studies will aim to test and possibly prove advantages of the invention relatively to the current costs for patients, hospital, society.

6 DISCUSSION

Based on our experience of ideation from a clinical uncovered need, formalization of an innovation, development and testing, we would like to share interesting points that guided us and seems conditions of success for bringing innovation in care and in medical devices field, which guid by definition to complex projects.

6.1 Guiding Principles

Team effort was a key in our pathway to a concrete solution: clinic, clinical research, technology, regulations, ethics, usability, market / business strategy, intellectual protection, project management… are skills hardly or not often grouped in the context of an hospital, or of medical devices field which is oftenly represented by small medium enterprise.

Contacts need to be actively researched outside, and realized with experts motivated to answer the questions and develop the specific project with anticipation and relevancy. Else the innovation risks to encounter the "death valley" located between research and real life.

Related to that, the time and money are important to anticipate. As we speak about little team, we can imagine the consequences of timelines like the ones we presented here, onto the survival of the start-up if not planned with a strong and realistic vision.

6.2 Some Tools?

Developing innovation in health is a field on which theory and models exist. Well known scales such as Technology Readiness Level (TRL, Scar Wars being today at a TRL 6-7), declined in Market RL, Financial RL… can provide accurate marks for emergence, development, maturity.

We can also refer to more dedicated ones to health such as CREPS cycle (Concept, Research,

Evaluation, Product, Care, Moreau-Gaudry A et al. 2010), Innovation RL, health tech innovation cycles (Center for Integration of Medicine and Innovative Technology - CIMIT, Boston) that take into consideration the dimensions of technology, regulatories, market, clinics…

Projects have also been provided on the subject, let's cite for example the European Itech "Roadmap for Research and Innovation in Health Technology" (FP7-HEALTH-2013-INNOVATION-1, CSA-SA – https://cordis.europa.eu/project/id/602667/fr), that describe 5 phases from need to industrialization, leading to 5 outcomes from proof of concept (POC) to reimbursment and commercialization.

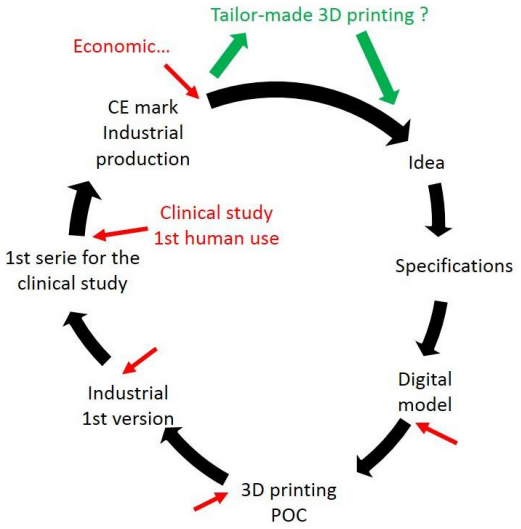

Figure 3: Scar Wars cycle of development.

The idea is to try using the scales/tools to define the project roadmap from the beginning, to anticipate the stages, duration, money needed, and to evaluate its progress regularly.

We proposed on Figure 3 the cycle of development of our innovation, with 7 steps from idea to industrialization, evaluations indicated in red, and perspectives in green.

7 CONCLUSION

The aim of the SCAR WARS project was to evaluate the effectiveness and safety of an innovation in the treatment of specific pathology on a targeted body location.

The device is proposed in addition to the usual care of patients seen at surgery departments, and will provide, at the level of the lesion, a controlled physical compression, reported in the literature as being a determining factor for the reduction of the volume of the scars and the rate of recurrence after reconstructive surgery.

The conclusions of the work carried out during the project will make it possible to lay solid foundations for the valorization of the device. Above all, the original and multimodal approach of evaluation could help identify new areas of improvement in the pathology management, and provide to the community new scientific data for a better understanding of these scars, and possible successes or failures of proposed treatments.

This first study will quickly provide the patient with an inexpensive device, with targeted properties of aesthetic, comfort and adjustability by the patient himself (within the limit of the maximum number of magnets imposed by the clinician). Those characteristics are hoped to be source of better compliance and therefore efficiency. The expected decrease in recidivism rates could result in a reduction in public health costs for resumption of resection, which could be evaluated with specific methodologies late. Adaptation closer to the morphology of the patient, or to other areas of the body by 3D printing can then constitute a potential opening of this project.

In terms of a more global approach and for an ambitious project, we tried to enhance the key important guidelines; general schedule of the pathway of innovation could be resumed by:

-writing of the project and the general objective: state of the art, context (points to improve), positioning, with clinicians and experts in the field;
-describing the solution (s) to be developed, broken down into several lots (technical, regulatory, tests (pre- and clinical, pre- and post-market…), business marketing, etc.), and players to be brought up at each stage.
-formalizing a consortium accordingly: do we have all the internal or external actors identified for the different stages ?
-establishing the budget (and means of search and obtention) accordingly.

One of the first deliverable of any project could be this master roadmap document, adapted and improved all along the life of the project.

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Contribution of Methodologies Adapted to Clinical Trials Focusing on High Risk Medical Devices

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Keywords: High Risk Medical Device, Evaluation, Clinical Trial, Adaptive Trial, Bayesian Statistics, Methodology.

Abstract: High risk medical devices clinical trials are complicated, expensive, time-consuming and need an improved clinical evaluation with better scientific evidence throughout the European Union. The purpose of this study is to identify methodologies whose use could facilitate the evaluation of the medical device. Adaptive methods and Bayesian approaches are expert tools that can accelerate access to innovation providing more flexibility but they are insufficiently used because of a lack of expertise and training in the trial community (clinicians, statisticians and regulation authorities). Involving stakeholders (regulation authorities, industrial, clinicians, biostatisticians, end-users) early in the conceptualization of the adaptive design improve adoption, implementation, feasibility and overall quality of that trial.

1 INTRODUCTION

The clinical evaluation of a new medical device is an essential stage in the industrialists' pathway towards market access. The new European regulation (MDR 2017/745) will be fully in force in May 2020 and requires clinical investigation particularly for high-risk medical devices (HRMDs).

Randomized controlled trials (RCTs) have long been recognized as the gold standard for evaluating the effectiveness of drugs. Conducting an RCT takes a great deal of time and financial resources, and great rigour in trying to isolate the specific effect of the intervention under study. Compared with drugs, HRMDs have specific features such as long-term use and unknown interactions with the human body, the means of explanting and replacing implantable devices, the user's skills, the human-machine interface, the management of data-flow generated, etc. These specificities require specific evaluation methods to generate better clinical evidence. Adaptive methodologies have been developed as an alternative to the traditional RCT design.

Even though the legislation, particularly American legislation with the Food and Drug Administration (FDA), qualifies adaptive methodologies as "modern" and "new" methods, a large number of these concepts are old and have remained unused for many years faced with the hegemony of RCTs.

The use of adaptive methods in designing clinical studies has become a major challenge to the evaluation of the safety and efficacy of a medical device, faced with the specificities of the field and the significant financial and temporal restrictions of this industry composed mainly of start-ups and SMEs. To do this it is necessary to find methods that take the specificities of the medical device into account. Several types of clinical studies may be carried out according to the different phases of the device's development.

The clinical phase is generally split into two stages, a first stage of collecting information about safety and performances of the device. This information is collected during feasibility studies or clarifications (implantation technique, patient characteristics, judgement criteria) and a second stage to evaluate the device's clinical efficacy in pivotal evaluation studies to demonstrate the risk-benefit ratio.

This work consists of reviewing methods that may be used in the clinical evaluation of high risk medical devices.

2 CLINICAL INVESTIGATION

Rather than "clinical trial", the term "clinical investigation" is generally used in Europe in reference to research on medical devices. The expression "clinical investigation" is thus defined in the ISO 14155 norm, "Clinical investigation on medical devices for human subjects", as being "... any study systematically designed and planned for use on human subjects, undertaken to check the safety and / or performance of a specific device." The term "clinical investigation" is defined in a slightly broader way in the American regulations (42 USCS § 1320a-7h (e)) as being "any experiment involving one or several human subjects, or products arising from the human body, and in which a drug or medical device is administered, dispensed or used."

Clinical investigations are subject to scientific and ethical examination. The protocol for clinical investigation includes justification, objectives, design, methodologies, control, how to conduct the clinical investigation and the documentation relative to results and the analysis method concerning it. The level of evidence of a study is characterized by its capacity to answer the question being asked. The randomised controlled trial is the experimental plan that offers the highest level of evidence to demonstrate the efficacy of a device relative to a gold-standard therapy. However, certain specificities of medical devices make this type of trial difficult to perform.

The main limits of resorting to a randomised controlled trial for medical devices are the impossibility to randomise patients, the device's short life-cycle, the small size of the target population, the difficulty of double-blinding, the low acceptability of patients and practitioners, the choice of comparator and the operator-dependent nature of the medical device.

Besides, classical trials are often long, which is incompatible with the evaluation of the medical device whose life-cycle is short and this can hinder access to innovation. When the trial is non-conclusive, this leads to the inclusion of lots of patients in a pointless trial with inefficient treatment. When the trial is conclusive with a very effective device being tested, this poses the problem of patients in the comparator group not having the chance of access to progress and delayed access to progress.
For medical devices designed to compensate for handicap, there is a potential loss of quality of life for the patients who might be able to benefit from them.

Clinical trials may be expensive and this deters certain small and medium-sized medical device companies which, in turn, delays or prevents access to new technologies and medical progress for patients and users. It is therefore essential to find new methods of clinical investigation centred around all these issues.

3 ADAPTIVE METHODS

3.1 Guides

The first part of this work consisted of gathering all the available guides in the field of clinical evaluation of medical devices, and publications on that theme. The following works were used:

- ✓ Methodological choices for the clinical development of medical devices; HAS evaluation report dated October 4th, 2013.
- ✓ Methodological specificities of the clinical evaluation of a connected medical device (CMD); HAS report on the elaboration of the guide on the specificities of clinical evaluation, in view of its access to reimbursement dated January 29th, 2019.
- ✓ Bernard A, Vaneau M, Fournel I, Galmiche H, Nony P, Dubernard JM. Methodological choices for the clinical development of medical devices. Med Devices (Auckl). 2014 Sep 23;7:325-34.
- ✓ Guideline on clinical Trials in small populations; Committee for medicinal products for human use on 27 july 2006.
- ✓ Guidance for the use of Bayesian Statistics in Medical Device Clinical Trials; Guidance for industry and FDA Staff on February 5, 2010.
- ✓ Adaptive Designs for Medical Device Clinical Studies, Guidance for Industry and Food and Drug Administration Staff, Document issued on July 27, 2016.

3.2 Improve Acceptability by Doctors and Take into Account the Operator-dependent Nature

When one arm in the study is less attractive than the other, studies may be carried out according to a Zelen plan or according to a complete cohort pattern. These types of trials introduce flexibility in the attribution of treatments and allow better acceptability of the randomisation by the patients and also give us the possibility of adjusting the results to the randomisation.

Zelen Plan (Zelen et al., 1983, Zelen et al. 1990)**:** The patient's consent is only requested for the new treatment and not for the gold-standard treatment

(simple consent). It is also possible to ask the patient randomised to the experimental group what treatment he/she wants to receive and to give him/her that treatment, or even in each arm of the randomization, ask which treatment the patient would like and to give the patient the treatment he/she wants to have (double consent).

The patients are analysed in the groups to which they were initially randomised and not in the arms of the treatment being received. This plan is only valid if there is not too great an imbalance between groups; that is to say, few patients leaving the study (if these are not related to the treatment) and if the changes of are not very frequent (fewer than 10% of patients changing arms).

This type of pattern might be useful in the high risk medical device area particularly when the target population is small and you think the recruitment is going to be very difficult as in the case of studies focusing on an implantable device (implanted for a more or less long duration, possible withdrawal / difficult withdrawal / very difficult withdrawal / impossible withdrawal) or an invasive surgical technique with a less invasive or less restrictive reference arm (with a drug alternative for example).

Comprehensive Cohort Study (Kearney et al., 2011, Torgerson et al., 1998)**:** the pattern consists of randomising all patients eligible for research and, at a second stage, given the patients who refuse randomisation the treatment they refer. In methodological terms the main pitfall concerns the absence of group comparability. However, it is possible to adjust the results on the randomisation.

3.3 Improve Acceptability of Doctors and Take into Account the Operator-dependent Nature

When certain centres only use one of the two techniques under study and do not know the other technique or only master the one technique and the result is operator-dependent, it is possible to use a trial based on expertise or a cluster trial (or a Stepped Wedge Cluster trial) to increase the participation of doctors and the reliability of the evaluation.

Trial based on Expertise (Devereaux et al., 2005)**:** in this case the patients are randomised to the doctor or team that masters the intervention or technique (for example, prosthetic hip implant surgery). The doctor only performs the procedure he fully masters. In this case, the doctor is device user and he is directly involved in evaluating this. For each study arm, the doctors master the technique that they are going to use and have reached the technical plateau, which avoids any imbalance between the two groups of the trial during the evaluation and is also more ethical. This type of trial is still little used. It is very pertinent when the techniques are different and complex.

Cluster Trials and SWCs (stepped wedge cluster) trials (Barker et al., 2016)**:** With this type of trial, groups of individuals are randomised (hospitals, services, care units, doctors) and not individuals. SWC trials are suitable when you want to gradually implement a new strategy or a new technique without going back to the previous one.

Centres start with the gold-standard technique and the time when each centre switches over to the new technique is randomised. The group experimenting the new technique can be compared both to itself based on the initial measures performed on that group and with the measures from the other patients who are using the gold-standard technique (independent, homogeneous control group).

This type of design may be useful when evaluating a new device, a new technology which is to be gradually introduced (for example a new device which is too expensive to use over several centres in the same area) but the number of clusters must be sufficient to ensure sufficient statistical power and the participation of centres/ services/ doctors must be good especially as these trials may be long (monitoring of inclusions and motivational strategy to be established on the scale of the cluster).

3.4 Compensate for a Small Target Population

When the target population is small, it is important to optimise and maximise the information collected on the patients in the study. In some cases, it is possible to test several strategies on the same patients.

Cross-over Trial (Fuehner et al., 2016, Haddad et al., 2010)**:** In this type of trial, each patient receives two study treatments (or more according to a factorial design). A weaning period is provided for after the patient has been given the first treatment. It is the order of administering the sequences of treatment that is randomised. This type of design is suitable for stable pathologies and when judgement criteria can be read independently over the two periods. The interest of this type of design is divide by at least two the numbers planned for the trial and therefore reduce the duration of the trial. This type of trial may be proposed in cases of evaluating high risk devices whose installation and use are not operator-dependent or if the technical plateau has been reached for all the investigators before setting up the trial.

SnSMART Trial (Small n Sequential Multiple Assignment Randomized Trial) (Tamura et al., 2016, Wei et al., 2018, Meurer et al., 2017)**:** This type of trial can be used when a patient is likely to receive several therapeutic sequences until he/he achieves the treatment aim (complete recovery, remission, etc). The sequences are predetermined beforehand and at the end of each sequence the randomisation is adapted to orient patients either to pursue their ongoing treatment if the response is favourable or to use one of the alternatives being tested in the event of non-response. The number of arms being tested may be adapted, if an arm turns out to be ineffective, it can be removed. These trials potentiate the numbers and may be used in cases of pathologies focusing on small target populations (SnSMART). This type of trial is interesting because it uses the information from the different sequences to compare therapeutic strategies and leads to the inclusion of fewer patients.

3.5 Introduce Flexibility to Take Technological Evolution into Account and Accelerate and Optimise Clinical Development

In order to take technological evolution into account and accelerate clinical development and product launching whilst allowing early terminations (futility/efficacy) or protocol adjustments (evolution/suppression of an arm), it is possible to use tracker design trials, sequential trials, MAMS trials and adaptive trials (detailed further on).

These trials rely on planned intermediate analyses which allow the investigator to glean information which is useful for adapting the development strategy. They are particularly interesting in the context of clinical evaluating medical devices.

Tracker Trial Design (Lilford, et al., 2000)**:** This type of trial was proposed to evaluate new technologies. The principle consists of following the evolution of the technology in the trials based on flexible protocols without a duration of numbers fixed beforehand and based on information obtained during intermediate analyses. It is therefore possible to interrupt a trial early on if the technique is efficient, detect poor performances and guide new developments.

Sequential Trials (Hamilton et al., 2012)**:** The principle of sequential trials consists of planning intermediate analyses in order to be able to conclude early on. The conclusion focuses either on the very high efficacy/tolerance of the experimental arm compared with the control arm if the results observed on the first patients are very promising, that is to say, beyond what was initially expected, or on its inefficacity (futility) if the results observed are below what was initially expected. With this type of trial, it is possible to quickly conclude on the main criterion.

Multi-Arm Multi-Stage trials (MAMS) (Simon et al., 1985)**:** MAMS trials are used in the context of a medical device's accelerated development plan. In fact in this type of trial, sequential trials are gathered into one single protocol (Redman et al., 2015) (e.g.: several competitive devices with one control arm).

The control group is not obligatory but it is recommended. The attribution of patients to each arm is randomised. The arms which do not fulfil the conditions for minimum efficacy (futility) during the intermediate analyses are removed and only the most efficient arms are retained. The first phase is not directly comparative, the second phase gives us the probability of selecting the best treatment compared with the others and the control arm is used to "estimate" the size of the effect.

4 ADAPTIVE TRIALS

4.1 Principle

With adaptive trials it is possible to modify items in the protocol during the study, based on data collected during the planned intermediate analyses without compromising the integrity and the validity of the study.

With adaptive methods it is also possible to strengthen the clinical evaluation of medical devices by authorising the analysis of lots of evaluation criteria, carrying out several intermediate analyses, early terminations in the event of inefficacity, allocating patients to the most promising arms, re-evaluating the sample-size and, more especially, redefining the target population.

These methods also make it possible to combine the early exploratory phases with the demonstrative phases which may make it possible to accelerate and optimise the development and implementation of innovative devices.

It is also possible with these methods to optimise the feasibility phases and confirmatory phases by, proposing much broader, adaptive feasibility trials leading to better-sized pivot trials or by proposing adaptive confirmatory trials testing several hypotheses as required, which would reduce the number of feasibility studies throughout the course of the product's development.

Group sequential design and adaptive sample-size adjustment were used frequently to make study

durations shorter and include a smaller number of subjects.

These methods may therefore make it possible to reduce the requirements in terms of resources, time necessary to finish the studies and increase the chances of the study's success.

There are several possible types of adaptation.

4.2 Response-adaptive Randomization Trials

The aim of this type of pattern is to treat a maximum number of patients with the best treatment under trial and to minimize the number of subjects necessary in the trial by introducing the possibility of an anticipated stop.

It may also be used in trials with several arms. It involves first randomising the patients with a balanced ratio then, gradually and throughout the trial, based on information gathered during the intermediate analyses it is possible to modify the affectation ratio in order to orient more patients towards the most effective treatment (Jiang, F, et al., 2013).

This type of design is an alternative to the multi-stage multi-arm (MAMS) trials seen above (Wason et al., 2014, Wathen et al., 2017).

4.3 Sample Size Reassessment Trial

At the time of the intermediate analyses it is possible to re-evaluate the number subjects necessary for the rest of the trial if the effect observed seems less than what was expected at the beginning of the trial (Magirr et al., 2016).

A misspecification of the expected treatment effect may result in an underpowered or overpowered trial. In the flexible framework, the remainder of a design can be modified at an interim analysis.

In an adaptive trial it is therefore possible to recalculate the number of participants and to increase the power of the trial based on new hypotheses without compromising the validity of the study.

4.4 Seamless Trials

These are trials for which the feasibility and pivot phases follow on from each other in the same trial (Thall, 2008). The two phases are based on complementary criteria (for example: survival without progression and overall survival).

Certain arms can be removed due to inefficacity and only the most powerful arms are pursued in the pivot study.

One control group may be included at the beginning of the pivot phase or before it.

4.5 Adaptive Enrichment

These are trials for which we observe, during an intermediate analysis, a better response to treatment in one of the sub-groups of patients (Simon et al., 2013, Lai TL et al., 2019).

The underlying idea is therefore to study the effect of the treatment in the sub-group whose size is not suitable for analysis beforehand. The eligibility criteria for the trial are modified and the sample-size is recalculated so that the size of the sub-group is sufficient in each arm.

5 BAYESIAN METHODS

5.1 Principle

Bayesian approaches may be used to implement and analyse clinical trials. They are used because they give the possibility of combining information obtained before the trial "prior information" (previous studies, expert opinion, literature…) and information obtained during the trial "current information" to formulate or reformulate a rule for decision-making.

In a Bayesian clinical trial, any uncertainty about a parameter is described according to probabilities, which are then updated during data-collection for the trial. The probabilities are set beforehand based on previous data and the probabilities are estimated *a posteriori* from the data obtained during the trial. There are no statistical tests but the probability of the treatment under experimentation being effective has a 95% credibility interval. However, it is very important that the *a priori* information used does not influence the final result too much (sensitivity analysis required). The quality of information supplied *a priori* is therefore a key element in the credibility of results**.**

5.2 Bayesian Medical Device Trials

Bayesian methods has been supported by the US Food and Drug Administration's (FDA) Center for Devices and Radiological Health for medical device clinical trials and are used in trials on medical devices (Pennello et al., 2008, Campbell et al., 2011, Campbell et al., 2016).

Pennello et al. 2008, explain how these analyses are particularly suitable in this case: "Device trials

can be particularly suitable for Bayesian analysis. For example, if a therapeutic device has evolved in relatively small increments from previous generations of the same type of device, then prior information from the trials of the previous devices can be predictive of the safety and effectiveness profile of the new device (Allocco et al., 2010). The reason the previous trials can be predictive is that the mechanism of action of a therapeutic device is often physical, implying a local effect that is often predictable. In contrast, the mechanism of action of pharmaceuticals is pharmacokinetic, implying systemic effects from similar but not identical formulations, which are often unpredictable. Other potentially reliable sources of prior information for device trials include clinical trials of the device conducted overseas, patient registries, pilot studies, studies of the device on similar patient populations, and perhaps nonclinical studies. Historical controls can also represent prior information for the control arm of a randomized controlled trial".

The information collected beforehand is generally based on previous studies on the same device or on a similar device ideally under similar conditions of use (same technique used, training of similar doctors with the same experience), on the same target population with the same type of management; it comes especially from designers (engineers), users (clinicians, patients) and the academic world (experts).

They are a more flexible alternative to classical methods (frequentist approach). They are used to adapt the randomisation according to the responses observed (see Bayesian adaptive randomisation). These methods also make it possible to compare several sub-groups of patients, several criteria, several time sequences because multiplicity is managed better Bayesian statistics. It is also possible to take missing data into account and to predict an event depending on what has been observed in other patients throughout the trial. The underlying hypothesis is that the patients of a same centre, a same trial or a same group of trials focused on the same device or on a similar device are interchangeable. Meta-analyses also use Bayesian methods to take into account the heterogeneity between trials and between groups of trials (for example several versions of the same device).

6 DISCUSSION

In this review, we noted that there have been many adaptive methods for decades, but their use is recent and mainly in the pharmacological area. Adaptive methodologies have most often been used in oncology.

Adaptive methods may respond to the specificities of clinical investigations on high risk medical devices. Nevertheless, so far they have been very little used in that area (Ribouleau et al., 2011) even though a few published examples can be found in the literature. This observation may also come from a more general situation concerning medical devices which most of the time are released without having undergone a proper clinical investigation. And even though since 1993 the European ruling has mentioned the obligation for each new medical device, whatever its risk category, to undergo a clinical evaluation to obtain CE marking, few clinical studies are indexed before they obtain the CE mark in Europe.

These "new" methods have encountered many suspicions, and the regulatory authorities in charge evoke methodological failings or data-collection problems specific to adaptive designs, which delay the process of product approval. The FDA and the EMA have had mixed experiences with adaptive designs (Collignon et al. 2018, Elsäßer et al., 2014).

Experiences have shown that applicants need to meet early and often with regulators. Adaptive design and Bayesian clinical trials need to be prospectively designed and require extensive pre-planning and model-building from the prior information to mathematical modeling.

Involving regulation authorities early in the conceptualization of the adaptive design improve adoption and implementation of that trial.

Adaptive design and Bayesian clinical trials require highly technically trained statisticians and programmers. A particular pedagogical attention should therefore be paid to accustom all the stakeholders, and particularly the scientists in charge of regulation before and during these trials, to these new uses of new methodologies.

7 CONCLUSION

Overcoming methodological difficulties in conducting clinical trials is a major challenge. Barriers encountered in the field of medical devices lead stakeholders to use new methodologies.

Adaptive methods could be used and has been the subject of several recent reviews (Bothwell et al., 2018).

Besides, various studies explored specific aspects of adaptive trials (Guetterman et al., 2017), including attitudes and opinions regarding confirmatory

adaptive clinical trials and obstacles to using them (Meurer et al., 2016, Guetterman et al., 2015).

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Place of High-risk Medical Devices in European Recommendations with a Focus on End-users

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Abstract As shown by recent incidents and scandals related to the use of high-risk medical devices an adapted regulation throughout the European Union is important. The European directives and the regulation issued by the member states include recommendations which apply to high-risk medical devices. The present study aims at collecting the recommendations regarding high-risk medical devices and specific to each country. Legislation, guidelines, scientific publications and grey literature have been searched. Different trends seem to appear in the states with the most advanced legislation: an increase of controlled trials, a better traceability, development of specialized registries, an improved vigilance system and an increased involvement of end-users. Although poorly present in the legislation, the end-users are more and more integrated to the development process of medical devices. Ergonomics and user experience can be seen as key factors of a successful medical device. Several important issues are stressed regarding the training and information of healthcare practitioners for implantation of the medical device and its initial setting if required. New avenues have also to be envisioned such as context of use analysis and user-centred design.

1 INTRODUCTION

Medical devices cover a wide range of products ranging from eyeglasses to active coronary stent, via wheelchairs. Medical devices are also characterized by a short life in the market, small patient populations and a high potential for innovation.

Due to medical advances and to recent scandals new European Union (EU) legislation was launched in 2017. This new regulation has led to the deployment of a transition period during which manufacturers may choose to refer to Directive or Regulation. Each country of the EU has transposed the directive into its national texts and has treated the fallout from recent scandals in a manner specific to its health and vigilance system. As a consequence, the guidelines and the recommendations for high-risk medical devices are uncoordinated and treated in different ways throughout the EU. For example, the recommendations for the surgical revision of Metal-On-Metal (MoM) hip replacements vary according to the different regulatory authorities: some rely on a specific protocol, other on blood metal ions. (Matharu et al.2018).

The diversity of medical devices, their increasing complexity, as well as the development of devices for personal use have increased the risk associated with misuse. There is a very wide variety of user profiles and a lot of attention is paid to end-users.

End-users are considered to be people who interact with or who manipulate the medical device. There can therefore be more than one user of a medical device. Among these, a distinction between professional users and non-professionals (Shah et al., 2009) can be made.

The degree of interaction between the patient and the device may vary. For example there is no interaction for a pacemaker, but the interaction is of capital importance in the use of some devices such as injectors, or pumps intended for administering drugs. The same goes for devices requiring changes or recharging of the battery or having a control interface.

Manufacturers are increasingly integrating patients to the development of products before they enter the market. This approach is considered to be safer for the patient and result in more effective devices (Martin et al., 2006). In addition, the awareness of handling errors made it possible to

envisage the usability of medical devices as an integral part of their development.

A major trend is to move from isolated end-user, as in traditional clinical evaluation, to patient groups and focus groups.

The use made by "operators", by health professionals must also be carefully evaluated to reduce the risk of incidents. Finally, the global environment (care structure, etc.) must also be taken into account. The concept of user experience indeed takes on its full meaning by aggregating the factors linked to the end-user, the device and their environment.

The aim of this work was to scan the regulatory environment and the development phases of a medical device. The benefits as well as the potential challenges to integrating the users' point of view into the clinical evaluation medical devices will be discussed. Then, examples from different countries of the European Union will illustrate what can be done. Finally a discussion will focus on European disparities with regards to the place of users.

2 CONTEXT

2.1 Regulations

The legislative framework has been developed on the principle of the new approach, the principle from the 1980s which provides for the approximation of laws between states.

Until 2017, three directives were available:

- Directive 90/385 / EEC (EUR-lex, 1990) of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices
- Directive 93/42 / EEC (EUR-lex, 1993) of June 14, 1993 relating to medical devices
- Directive 98/79 / EC (EUR-lex, 1998) of the European Parliament and of the Council of October 27, 1998 relating to in vitro diagnostic medical devices

Other more technical directives have been added as technologies evolved. For example, at the initiative of the French Presidency of the European Council, the general directives were revised by Directive 2007/47 / EC (EUR-lex, 2007). The clinical evaluation has been made compulsory, under the conditions specified in a new annex (in force in France in 2010).

These directives must be transposed into the national law of each country of the European Union (EU).

In 2017, two European regulations entered into force:

- Regulation (EU) 2017/745 (EUR-lex, 2017a) of the European Parliament and of the Council of 5 April 2017 on medical devices
- Regulation (EU) 2017/746 (EUR-lex, 2017b) of European Parliament and the Council of 5 April 2017 on in vitro diagnostic medical devices.

Immediately applicable, a regulation does not require transposition into national law.

Currently, in 2019 we are in a transition period, that is to say that a manufacturer may choose to mark a medical device EC Directive or under the new regulation.

Shortcomings of the current system are frequently described, some being strongly related to end-users:

- An inadequate declarative vigilance system and post marketing monitoring
- A lack of transparency and information sharing

2.2 High-risk and Medical Devices

Classification according to risk (class I, IIa, IIb or III) allows to get as close as possible to the concept of high risk. But high-risk and class III are not necessarily totally overlapping. Our point of view is that a medical device is considered as high-risk in case of:

- A sensitive anatomical location
- The implantable nature of the medical device

and / or

- The use of new technologies

and / or

- The use of new materials

2.3 Usability and End-users

2.3.1 End-users, Usability, and Suitability for Use

Users of medical devices cover a wide range of people, professionals or non-professionals. It can be the person responsible for fitting, adjusting the device, but also maintenance people, their families and caregivers in general (Shah et al., 2009).

Defining end-user is more difficult. End-users are people who interact with or manipulate the device. The term of end-users could restrict the previous list to the operators and to people who uses the device (the patient). End-users have a wide variety of profiles. Among non-professional users, a special place must be made for people with special needs, especially the elderly or disabled (Shah et al., 2009). It is noted that many of these users are likely to have disabilities hindering their use of medical devices or difficulties due to technological advances, in

particular with interfaces. Moreover, as stated in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA), “as healthcare evolves and patient care is transferred to the home or public environment, less skilled or even unskilled users, including patients and caregivers, must be able to use quite complex medical devices safely.” (MHRA, 2017).

The MHRA explains that Human Factor refers to how a person will interact with the systems surrounding them, including the technology they use. It often encompasses other terms such as ergonomics and usability.

The concept of usability has become increasingly important and combines ease of use and training. It is described as the characteristic of the user interface that establishes effectiveness, efficiency, ease of user learning and user satisfaction while usability engineering is the application of knowledge about human behavior, abilities, limitations, and other characteristics related to the design of tools, devices, systems, tasks, jobs, and environments to achieve adequate usability (International Electrotechnical Commission or IEC 62366:2015, International Organization for Standardization or ISO, 2015)

2.3.2 The Need to Take into Account End-users and Potential Barriers

The awareness of errors in handling medical devices has highlighted the need to place usability at the center of the development of medical devices.

The FDA recognizes the importance of usability and includes requirements in this area in GMPs (FDA, 2018a) and in other documents such as, for example, guidelines for designing interfaces for usability tests (Story, 2012).

Medical devices meeting users’ needs are described as safer (Kaye, 2000) (al., 2004). On the contrary, ignoring their needs can have disastrous consequences (Stone and McCloy, 2004).

Meeting users’ needs is known to (Martin et al., 2006):

- Improve the safety of devices
- Improve the usability of devices
- Reduce Device Recalls
- Limit the need for ad hoc changes
- Improve efficiency of users
- Improve patient outcomes and satisfaction

Knowledge based on user experience is a source of valid evidence which is used to complement the contribution of health professionals and researchers.

One could say that without this view "from within", the panorama of Research is incomplete.

In addition, taking into account the end-users’ point of view makes it possible to manage the expectations of this population, expectations which are often poorly understood, as well as the gap between these expectations and those of manufacturers and / or professionals.

Several barriers were however identified. The researchers, manufacturers may have difficulties to perceive the benefits of including end-users, especially if it is felt that they do not have the knowledge to understand or to help the Research process (Bridgelal Ram et al., 2008).

In 2007, Brideglelal at al. (Bridgelal Ram et al., 2008) made the following observation: “Although there has been academic research on user engagement, there is a lack of commensurate work on the practicalities of such engagement”. If the interest in involving end-users is no longer questioned, the way to do so remains generally insufficiently documented and there is a lack of evidence.

The difficulty of easily accessing end-users by manufacturers, in particular subcontractors, was underlined (Li et al., 2011).

2.3.3 Concrete Measures

Manufacturers resort to early consultation with professionals and non-professionals. This is even more crucial for high-risk medical devices.

The usability of devices must be evaluated by firstly taking into account the specific difficulties and limitations of end-users and in various environments (technological, social, etc.).

The user experience (UX) makes it possible to integrate the voice of end-users at all stages of medical devices development. Heuristic evaluations are carried out. Pillalamarri et al. describe it as building a highly usable, safe and efficient system that goes beyond the requirements of end-users (Pillalamarri et al., 2018). These same authors divide the user-experience evaluation into 4 distinct phases:

- The Research phase: identification of unmet needs
- The conceptualization phase: a synthesis of the identified needs is performed with a translation into specifications for the future medical device. It is at this stage that user groups are defined
- The design phase
- The test phase: prototypes are developed to simulate the product that will be marketed and then evaluated by potential users based on the identified patients groups described above

The authors explain that these phases are iterated until all the success criteria are met.

It is very important that people conducting research based on UX work with specialists in human factors or ergonomics in order to optimize medical devices for their use by the user and in the environment where they will be used. For medical devices, the human factor process is used to minimize the risks associated with use (formative assessment), and then used to confirm that these efforts have been successful and that users can use the medical device safely and effectively (summative assessment).

The FDA mentions the following benefits to applying HF / usability engineering (FDA, 2019):

- Easier-to-use devices,
- Safer connections between device components and accessories (eg, power cords, leads, tubing, cartridges),
- Easier-to-read controls and displays,
- Better user understanding of the device's status and operation,
- Better user understanding of a patient's current medical condition,
- More effective alarm signals,
- Easier device maintenance and repair,
- Reduced user reliance on user manuals,
- Reduced need for user training and retraining,
- Reduced risk of use error,
- Reduced risk of adverse events, and
- Reduced risk of product recalls.

Patients can also fill out moodboards, storyboards and participate in questionnaires on the creation of user interfaces, then test prototypes.

The instructions for use and labeling are also part of the measures that must be taken to lead to good usability of the medical device.

2.4 Our Research

2.4.1 Aims

Our goal was to identify the recommendations / guidelines issued in the countries of the European Union on high-risk medical devices. In this part of our work, we then focused our Research on the aspects affecting end-users.

2.4.2 Identification of Sources and Reading Documents

The sources consulted fell into two categories: scientific literature or gray literature. The latter type of literature refers to documents from governments, universities, companies, and organizations in the form of print and electronic media, and not controlled by commercial publication.

A list of authorities and national agencies for the 28 EU countries, then websites of interest has been drawn up, country by country. To this end training tool kits from the French Clinical Research Infrastructure Network (F-crin) site (European Clinical Research Infrastructure Network (ECRIN, 2019a)) and the F-crin campus (ECRIN, 2019b) were used, as well as documents from the World Health Organization (WHO, 2019).

The documents were then read, with a focus on end-users, human factors and usability.

Examples of recommendation targeting end-users will be presented below.

3 PLACE OF THE END-USERS IN THE EUROPEAN RECOMMENDATIONS

The end-users have an increasing role to play at various stages of the life of the medical device from its conception to its appropriate use which requires both adequate information and training. The role of end-users is also important in care-organization, traceability, registers and vigilance which are keys in the optimal use and monitoring of medical devices.

3.3.1 Patient Associations

According to the European Patient Forum (EPF), patient associations are partners providing feedback through stakeholder advisory groups, experts, public consultations or institutional meetings of the European and / or national government. Patient associations are able to help decision makers understand the experience of living with a given disease. They use this “end-user perspective” to promote the interests of patients at all stages of policy development and in a range of institutional contexts (EPF, 2017).

In France, for example, the High Authority of Health (HAS) has launched a number of patients consultations for some high-risk medical devices), like intracranial stents (HAS,

In the Netherlands, the General Inspectorate will initiate discussions with patient associations to carry out initiatives aimed at encouraging patients to report incidents and complaints to healthcare professionals and / or the healthcare facility concerned, in the case of MoM hip prostheses.

Patient associations are therefore consulted by various national or European bodies. It is very difficult to identify consultations of patient associations by manufacturers themselves maybe because confidentiality and intellectual property issues might have impacted the availability of data.

3.3.2 Co-design, Co-development, and Focus Groups

The European regulation states that: "Devices shall be designed and manufactured in such a way as to remove or reduce as far as possible: the risk of injury, in connection with their physical features, including the volume / pressure ratio, dimensional and where appropriate ergonomic features" and also that: "Any measurement, monitoring or display scale shall be designed and manufactured in line with ergonomic principles, taking account the intended purpose, users and the environmental conditions in which the devices are intended to be used "

The regulations insist on taking ergonomic characteristics into account at the design stage.

In spite of the limitations mentioned above, manufacturers use focus groups which integrate the science of user experience at the early stages of development of their medical devices.

Focus groups are small groups that intervene before the product is placed on the market. They allow (Bridgelal Ram et al., 2008):

- The definition of unmet needs
- The translation into development concepts
- Their validation by retroactive loops

Focus groups turn out to be very interesting and informative. They consist of small groups of selected people with whom interviews are conducted in the presence of a moderator. Lehoux et al describe these focus groups as comprising 6–10 participants and lasting between 1.5–2.5 h (Lehoux et al., 2006). According to the same authors, if the focus groups share characteristics of other qualitative methods, what makes them unique are the interactions that develop between the participants, and between the participants and the moderator.

No reference to focus groups was identified in this preliminary consultation of the gray literature on recommendations related to high risk medical devices.

3.3.3 Training / Information for Health Professionals

Many of these recommendations concern specific medical devices, generally those which have been the subject of questioning or controversy.

There are few more general recommendations that is to say that are not formulated in response to a given problem

- In Belgium

According to report 158 of the Belgian Health Care Knowledge Centre (KCE), particular attention must be paid to the qualification and training of health professionals (HulstaertHulstaert et al., 2011). This human factor will often contribute to the safety and then to the efficiency of the device in routine use and therefore influences the external validity of the test.

In KCE report 249, professional end-users are implicitly pointed out (Baeyens, 2015). It is mentioned that clinical practice recommendations may stipulate that specific interventions must only be carried out in specialized centers and by trained operators and teams experienced in performing complex procedures. In general, however, the immediate impact of such a measure after obtaining a CE label is limited given the time required to develop such clinical recommendations. In addition, these recommendations are not binding.

Information is the crucial element to allow the healthcare professional to consider the use of a device and to allow the patient to make an informed choice on this subject. The patient must therefore be properly informed of the risks associated with the use of a new high-risk medical device and of all the possible alternatives. Merely mentioning that the device has the CE label is not enough.

Health professionals may also be required to report to the authorities the use of a high-risk medical device in advance.

- In Austria

General recommendations have been identified:

According to Annex 1 of the Medizin produkte betreiber verordnung (MPBV) law, the devices for which special safety precautions must be taken include the external active components of the active implants (BASG, 2019). For these devices, the operator must perform an initial inspection (or have it carried out) before the first application.

The external active component intended for the patient being delivered only after the implantation operation, the operator must also carry out verification for this component.

- In France

There are no general recommendations on these aspects, but only in reaction to situations or concerning specific medical devices.

Several arrangements have been made regarding professional end-users for the placement or the removal of a medical device. For example, the decree of July 3, 2012 limits the practice of implanting aortic valve bioprostheses by transcutaneous arterial route or by transapical route to certain healthcare establishments in application of the provisions of article L. 1151-1 of public health code (Legifrance, 2012).

The decree of December 14, 2018 limits the practice of the act of explanting devices for tubal sterilization (ESSURE) to certain health establishments in application of the provisions of article L. 1151-1 of the public health code (Legifrance, 2018).

Associations, such as Euro-Pharmat, a voluntary association, put online sheets for the proper use of certain medical devices classes, such as for example skin substitutes (Euro-Pharmat, 2014) or catheters with implantable chambers (Euro-Pharmat, n.d.).

Recommendations to professionals also come from medical societies. The National College of French Gynecologists and Obstetricians (CNGOF) provides professionals with a technical file on the removal of ESSURE final sterilization implants as well as a data collection sheet to be used before and after removing the implant (CNGOF, n.d.). The professional board of plastic surgeons has issued recommendations relating to breast implants and the risk of anaplastic large-cell lymphoma, stressing that when there is no reasonable alternative solution, the benefits brought to patients by breast implants, both in reconstructive surgery and in cosmetic surgery, are currently infinitely higher than the risk of contracting this specific lymphoma (Directoire Professionnel des Plasticiens, 2018 Professionnel des Plasticiens, 2018). The HAS provides documents on “good use of health technologies” (for example on implantable spinal neurostimulators (HAS, 2014) or for coronary angioplasty (HAS, 2012).

The French National Agency for Medicines and Health Products Safety (ANSM) offers recommendations to healthcare professionals. This is the case of the recommendations intended for surgeons for MoM prostheses (ANSM, 2014).

- In the UK

The National Institute for Health and Care Excellence (NICE) has made guidelines available for a number of clinical situations (NICE, 2019), including implants for example:

- Transcatheter aortic valve implantation for aortic stenosis (TAVI) (NICE, 2017a).
- Leadless cardiac pacemaker implantation for bradyarrhythmias (NICE, 2018).
- Artificial heart implantation as a bridge to transplantation for end-stage refractory biventricular heart failure (NICE, 2017b)

- In the Netherlands

Many recommendations follow products for which scandals have broken out.

For example in the case of the vaginal mesh, the NVOG “Dutch Society of Obstetrics and Gynecology” in 2014 made recommendations for operators / team performing interventions with the mesh (not exhaustive) (NVOG, 2014):

- That the competent urogynecologist is the person carrying out the intervention. Anyone who has made at least 20 mesh placements is considered competent. For urogynecologists starting out with this technique, this experience must be acquired under the supervision of a competent urogynecologist. To maintain the quality of the placement, and after a satisfactory learning curve, it is recommended that the specialist performs at least 10 placements per year.
- That in the most complex cases it is advisable to refer to specialized centers

3.3.4 Training / Patient Information

The new regulations for medical devices stipulate (EUR-lex, 2017a):

"In eliminating or reducing risks related to use error, the manufacturer shall:

(a) Reduce as far as possible the risks related to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and

(b) Give consideration to the technical knowledge, experience, education, training and use environment, where applicable, and the medical and physical conditions of intended users (design for lay, professional, disabled or other users).

- In Austria

General recommendations have been found, in particular concerning active implantable medical devices (BASG, 2019):

The parts of the system which are given to the patient as a non-professional user must be handled by him/her in accordance with the manufacturer's instructions, a standard training of the patient being necessary.

The patient or, where applicable, his legal representative must receive information in

accordance with § 81 MPG: information on the implant, instructions for use, time when a professional must be consulted ... Furthermore, in accordance with § 81, paragraph 4 when patients are informed about the use of medical devices, it is necessary to take into account the instructions provided in the instructions for use.

As the patient is a “lay” user, this must be taken into account. It is the responsibility of the manufacturer to provide instructions for use, accompanying documents and other information necessary for safe use for the intended users.

After the implantation and the appropriate information of the patient by the person in charge of the implantation of a medical device, the patient becomes responsible for the respect of the dates of the medical visits of control, etc.

Patients and groups of users must therefore always be taken into account: infants, patients having suffered a stroke, patients suffering from mental and / or physical impairments, etc.

It is the responsibility of the manufacturer of the medical device / of the implant to establish appropriate instructions for monitoring the patient (duration, deadlines) and possible verifications. This also includes the need to establish an active reminder to patients about their appointments for follow-up exams (for example, by the treating physician or the health facility).

- In France

There are recommendations in response to events that have occurred for specific medical devices

For the ESSURE ® final sterilization device, the ANSM, the CNGOF and the Ministry of Solidarity and Health have made available a patient information sheet "You are a carrier of the ESSURE final sterilization device" (Ministère des solidarités et de la santé, 2018) and a "removal of ESSURE ® device" sheet (CNGOF, 2018).

The professional directory of plastic surgeons has posted files for breast augmentation for aesthetic purposes and for breast reconstruction (SoFCPRE, 2019), (SOFCRPE, 2019). The HAS made it possible to adapt the first sheet to provide answers on reconstruction: "Additional information to be included in the sheet intended for patients of the French Society of Plastic, Reconstructive and Aesthetic Surgery of April 2015 before the placement of a breast implant for cosmetic reasons” (HAS, 2015). The French Foot Surgery Association (AFCP) provides an “ankle prosthesis passport” for patients (AFCP, 2012), as well as an information letter (AFCP, 2012).

3.3.5 Care Organization

- In Austria

The implant (including external components if applicable) is under the responsibility of the healthcare establishment until implantation (from appropriate storage to controls recommended by the manufacturer). After implantation, the implant becomes the property of the patient and, from this moment on, the patient is considered as the "user" of this implant (BASG, 2019).

- In Belgium

The KCE report 249 (Baeyens, 2015) mentions the limitation of routine use of specific medical devices to reference centers. Belgian hospital law already provides for the possibility of using referral centers to guarantee a high level of quality of care. The obligation to reserve the use of high-risk medical devices to a limited number of healthcare facilities for a certain period could in some cases be justified.

After placing on the market, reference centers may be asked to carry out an "appropriate study" (eg RCT) - with an assessment of proportionality on a case-by-case basis.

- In the Netherlands

In the context of vaginal mesh, recommendations were made by the NVOG “Dutch Society of Obstetrics and Gynecology” in 2014 for the structure that offers this type of intervention (not exhaustive) (NVOG, 2014):

- That at least two Gynecologists with a sub-specialization in urogynecology, competent in mesh surgery are present in the institution.
- That the structure engages in a quality assurance approach which is specific to this use
- That the structure registers the implant and records any complications in a database allowing the national scale monitoring of patients based on the social security number.

Recommendations intended for collaboration with manufacturers (not exhaustive):

- The introduction of new materials should only take place within the framework of studies.
- The studies will be coordinated and approved by the Urogynecology Consortium. Observational studies require a minimum of 118 participants, with at least one year of follow-up
- Complications must also be reported by the practitioner to the company that developed and marketed the product.

3.3.6 Traceability

Steps have been taken in Belgium where all implant placements lead to their registration on the central register of traceability. The medical devices plan, a public health improvement project in Belgium, aims to improve traceability. On June 15, 2015 the French Care Supply Branch (DGOS) made general recommendations as well as recommendations to the hospital care system (DGOS, 2015).

3.3.7 Registers

The creation and the keeping of the registers is the most represented recommendation found in the EU countries, and there is currently a wave of creation especially for breast prostheses.

The setting up of registers can be seen as a measure oriented towards end-users because it requires the active participation of the operators and of the patients

The Scandinavian countries have a culture of registers; some of them focusing on high-risk medical devices. The first ever created register was collecting information on joint replacement. The establishment of such records is considered to have lowered the hip prosthesis revision rate in Sweden (Herberts and Malchau, 2000). The creation of new registers (Lyratzopoulos et al., 2008), (or the revision of existing records) should include a reflection on the filling system (mandatory? Voluntary?). This should be complemented by consideration on the patient's consent to extend its data and on the criteria to be met to get enough information, while respecting the protection of patient data.

3.3.8 Medical Devices Vigilance

Countries agree that the system suffers from significant underreporting. However, no specific recommendation for high risk medical devices was found. However, it is suggested to encourage health professionals to report incidents to manufacturers. Databases listing the incidents are available but most of the time, their access is not public or restricted.

The MAUDE (Manufacturer and User Facility Device Experience) database in the USA allows patients to make their own statements (FDA, 2019b). It is probably a very interesting opening on the role of patients as end-users

4 DISCUSSION

This work illustrates the growing awareness of the role of end-users in medical high-risk devices in Europe. Very recently, and for example in France, the HAS (HAS, 2019) and ANSM (ANSM, 2019) have initiated patient association consultations and public hearings to consider the patient's voice.

The place of the end-user is unequally represented in the recommendations of various European countries. As with other types of recommendation, most of them were issued following incidents affecting specific medical devices. For example, this is the case of the vaginal mesh for which the Netherlands have issued a number of recommendations for professionals [32]: peer-training, "minimal" number annual implantations, specialized centers ... It is the same for hip prostheses with metal-metal friction couple (Inspectie Gezondheidszorg en Jeugd, 2015) (GOV.UK, 2017), or the Essure ® device mentioned above. Most of the documents found were concentrated in France, Belgium, the UK and the Netherlands. Belgium and Austria have issued more general guidelines about the training / information of patients and health professionals. The Nordic countries have further developed the registers. This requires an active role of professional and patient involvement.

Another point worth highlighting is the work provided by academics and professionals. Although little or not mentioned in the texts and recommendations issued by the authorities, networks of professionals have organized themselves to best address the question of end-user. For example, in France, the Clinical Investigation Centre for Innovative Technology (CIC-IT) network was set up in 2008 by the Inserm and the Ministry of Health (CIC-IT, 2016). Recent and creative initiatives have emerged such as living labs. Living labs are based on user-centered methods which operate in real-life conditions. As a result, patients are involved in the co-developement of innovations from the very beginning. ENoLL, the European Network of Living Lab is the international, independent non-profit association of bench-marked living labs with more than 340 accredited living labs worldwide characterized by its diversity and multidisciplinary perspective (Europeana, 2014). The involvement of patients in an approach gathering companies, academics and research centers such as that promoted by EIT Health is of importance. It is worth to note that some initiatives are developed by patients themselves e.g. the European Patients' Academy on Therapeutic Innovation (EUPATI).

A question remains to be answered: is the harmonization at the European level desirable? For example, would it be advisable to "delegate" the administration and collection of data from arthroplasty registers to countries having the best experience (Sweden, Denmark) or would it be desirable that each EU country takes its own register?

This preliminary work has limitations. First, translations of documents and the language barrier may have led to understanding defects. Then imperfect knowledge of health systems in each country may also have influenced the way to treat the subject. A certain degree of subjectivity, for example in drawing up of the list of sites of interest, is recognized. Finally, this work should be put in perspective with other fields such as methodology or economy, to get a more comprehensive view of the subject.

Maybe the main limitation of this study is to be centered on the way guidelines, focus groups or training are tackled by the European countries and their regulatory authorities. A new field of progress regarding the role of end-users is known as context of use analysis. This type of analysis is directed toward the intended users and associated constraints either technical or due to the environment of use. User-centered design is an innovative approach that remains to be applied to medical devices in order to promote their adaptation to all the various users' profiles, practices variability, working environment, and conditions of use.

5 CONCLUSION

The consideration of ergonomics is increasingly important, and its place will further develop. It seems important to stress that many agree on the fact that a medical device should be inseparable from the operator, from the recipient (patient), and from the care structure. Patient information, training / information of professionals and usability are the essential components.

As a consequence, the role of end-users in high-risk medical devices is a major public health issue. Significant progress is to be done and the recommendations have obviously to be adapted. New trends of medical devices development need to be included such as context of use analysis and user-centered design. It therefore seems necessary to develop new guidelines and recommendations. But the diversity of technologies and devices available is such, with the constant emergence of innovations that it is legitimate to consider if global recommendations are possible or even desirable.

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

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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 promotors (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 devices: 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.

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