Threats and Opportunities for the Clinical Investigation of High-risk Medical Devices in the Context of the New European Regulations

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Abstract: This position paper analyses the threats from the current situation of the clinical investigation to the expectations of the new European regulations focusing on high risk medical devices (HRMDs). We present also some opportunities to improve the feasibility and quality of clinical investigation. In summary, investigation protocols of medical devices, advised and authorized by the competent authorities, are few and heterogenous. There is a lack of quality in the existing studies, a lack of methodological knowledge and consequently high expectations for assistance from those involved in the design of clinical study protocols on HRMD. Guidance that is specific to the different type of devices is missing. Adaptive designs, pragmatic trial, usability methods, computer modeling and real world data are gaining more and more traction for assessing the safety and performance of high risk medical devices from a regulatory view- point.

1 INTRODUCTION

A series of major scandals have recently eroded public confidence in the way high-risk medical devices (HRMDs) are evaluated and monitored. Of course, these situations have led to the withdrawal of products from the market and legal actions have been taken to sanction not only unscrupulous manufacturers but also the notified bodies who issue the famous 'CE marking' required to introduce new products on the European market. By the end of 2018, the International Consortium of Investigative Journalists' 'implant files' investigation shed light on the way manufacturers can obtain the right to market medical devices in Europe. These situations highlight the weaknesses and failings of the health control system for launching and monitoring HRMDs. And yet, both patients and physicians want to ensure that knowledge on innovation can guarantee safe and efficient use of the new product.

New European regulations on medical device (EU Medical Device Regulation 2017/745) will come into effect in the spring of 2021. These new regulations set forth new, improved rules to strengthen clinical evidence, particularly for HRMDs for which clinical investigation is compulsory.

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This regulatory landslide represents a big challenge for European Health SMEs (some 25,000 companies, representing 95% of the MedTech sector in Europe) to maintain their competitiveness and capacity for innovation, with limited internal resources; especially in clinical trials skills. The impact of Medical Device Regulation (MDR) entering into force and the economic crisis linked to the Covid-19 on the sustainability of these companies has not yet been analyzed.

Updating clinical evaluation strategy and reports to meet the new European requirements will require major efforts for most manufacturers selling on the EU market. Given the wide range of medical devices (MD) available on the market and their countless variations in design features, treatment goals and targeted patient groups, setting a single standard study protocol seems unfeasible.

This paper analyses the threats arising from the current situation to the expectations of the new European regulations focusing on HRMDs. We present also some opportunities to improve the feasibility and quality of clinical investigation.

2 DEFINITION AND SPECIFICITIES OF HIGH-RISK MEDICAL DEVICE

Classification of Medical Device is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Three classes are defined, from Class I including devices with the lowest risk to Class III including those with the greatest risk (EU Medical Device Regulation 2017/745). Device classification depends on the *intended purpose* of the device, but also upon *indications for use* and *targeted population*. Class III devices usually sustain or support life, are implanted, or present potential unreasonable risk of illness or injury. Examples of Class III devices include implantable pacemakers and breast implants. Around 10% of medical devices fall under this category.

High-Risk Medical devices (HRMDs) correspond to current class III and implantable devices. Many tools based on the annex VIII of the MDR assist in the risk classification (class I, IIa, IIb or III) of the product. But high risk and class III are not necessarily totally overlapping. Other devices may be high-risk and a variety of factors can participate in the definition of a high-risk medical device, such as a specific anatomical location for its use, the implantable nature of the device, the use of innovative or untested technologies or materials. The implementation of any device can also be high-risk, due to:

- the vulnerability of the patient himself (e.g.: children, pregnancy, chronic disease, aged)
- the difficulty and delicacy of handling
- the operator's dexterity and experience (including the patient himself, his relatives or health care staff)
- the material environment in which the act linked to the device will be performed
- the potential complications of the procedure performed.

HRMDs have particularities that make the conduct of clinical investigations difficult, such as long-term use and unknown interactions with the human body, the means of explanting and replacing implantable devices, the human-machine interface, the management of data-flow generated, etc.

Although these issues are taken into account in usability standards (IEC 62366-1 and IEC 60601-1-6) and many methods of Human Factor Engineering (HFE) have existed for years, they seem to be underused (BSI 2016).

3 THREATS ARISING FROM THE CURRENT SITUATION IN EUROPE

3.1 The Loss of Europe's Attractiveness for Carrying out Clinical Studies

The complexity of the regulatory process for HRMDs is partly due to a significant fragmentation of the global market. Namely, many countries have their own set of rules around the world (Heneghan, 2012). A new device classified into Class III in Europe may very well be considered a Class II device according to a 510k procedure without the need for a clinical investigation in the United States, which is easier for businesses.

From our analysis (Figure 1) of annual declarations of interventional studies on the website clinicaltrials.gov, we note an increase of 16% worldwide for medical devices over the last five years (versus 9% for drugs), while Europe is experiencing stagnation in the number of studies on medical devices (+ 2%) and a decrease in the number of studies on drugs (-5%).

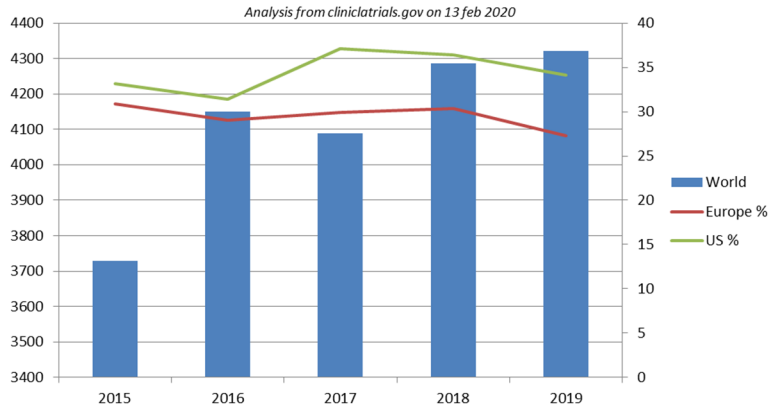

Figure 1: Evolution of clinical trials on medical devices worldwide and representative share for the USA and Europe (in %).

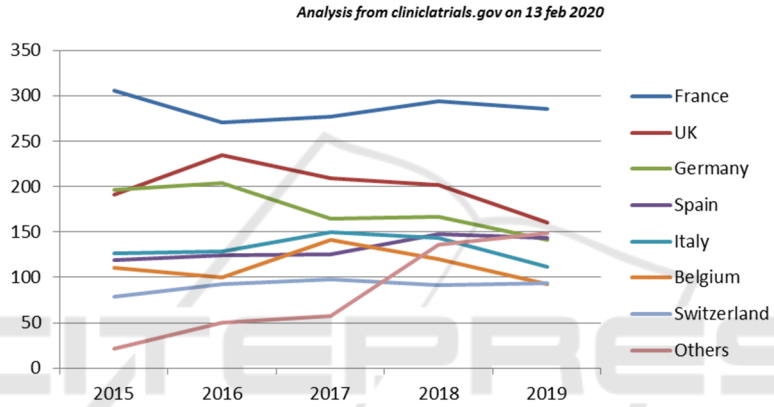

Figure 2: Distribution of Clinical trials on Medical Devices in Europe from 2015 to 2019.

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Overall, one study on a medical device starts for every 3 clinical trials starting on a drug. This has been stable over the last five years worldwide whereas, in Europe, this ratio which was identical to the worldwide figure five years ago, is now approaching a ratio of 1: 2 (3 medical device studies for 8 drug studies in 2019).

The figure 2 shows how the initiation of interventional clinical trials for medical devices has slowed down in the different member states of Europe (-10% in 2019 compared to the previous year), and in particular from the year of publication of the European regulation 2017/745, and the dropout rate in international competition, particularly in relation to the US.

3.2 The Current Observation on the Lack of Quantity & Quality of Clinical Studies on MD

Moreover, manufacturers have plenty of leeway and different interpretations in performing or not the clinical studies required to obtain their CE marking. Most of them do the clinical evaluation of their device based on data in the literature and assimilation with predicates already on the market. In 2017 the French health authority (ANSM) registered CE markings for more than 15,293 new medical devices (44% class II or III CE marks) while, at the same time, this same authority only issued 93 authorizations for new clinical trials of medical devices.

The Iqwig (Independent German Institute for Quality and Efficiency in Health Care) assessed the methodological quality of 122 medical device evaluation study projects submitted to the Berlin ethics committee from March 2010 to December 2013 (Sauerland 2019). Of these 122 studies, 69% were planned before marketing and 57% were randomized controlled trials (RCTs). While only half of the studies sought to demonstrate the effectiveness of the medical device, in the other studies the main objective stated was safety (18%), performance (12%), patient-related benefits, feasibility or user satisfaction.

A European study by Olberg et *al*. highlights the low level of evidence and the poor quality of studies in the files submitted for the registration of HRMDs with European technology agencies over the 2010-2015 period (Olberg 2017). Their results concluded that only 9% of these files had a very high level of clinical evidence (meta-analysis but most of them had pooled effect sizes driven up by a few randomized control trials (RCT) of low-to-moderate quality) and only 29% had a high level of evidence (RCT). Overall, 61% of clinical studies had a moderate to low level of evidence.

3.3 Imprecise Recommendations for Conducting Adequate Clinical Studies

The European Commission provides a range of guidance documents to assist stakeholders in implementing the regulations related to medical devices (MEDDEVs guides). These guides promote a common approach to be followed by the manufacturers and Notified Bodies involved in conformance assessment procedures. Revision 4 (MEDDEV 2.7/1 rev.4, June 2016) is more prescriptive and requires manufacturers to provide greater quantity and quality of information for clinical evaluations. The first set of guidelines (MEDDEVs guides) was recently updated and clarified by the European Commission's Medical Device Coordination Group (MDCG 2020). The MDCG posted new guidance (during the year 2020) on clinical evaluation and evidence for devices and postmarket clinical follow-up plans, representing for us the basis to be completed by future guidelines dedicated to HRMD:

However, these MDCG guidelines give general advice, and miss the operational details needed to adapt the design of studies and statistical analyses to the characteristics of innovative technologies. The most appropriate, least burdensome paths for gathering clinical data to support marketing approval for HRMDs are as varied as the devices themselves; so more operational guidance are needed.

With the exception of a handful of cardiology devices, available guidelines (from EU directives, MDCG newly edited guides or national transcriptions) and ISO/FDIS 14155 remain mostly vague and imprecise in describing how to conduct a clinical investigation and consider the clinical evidence. Instead, the guidelines let manufacturers choose how to create their clinical study protocols. The manufacturers in charge of evaluating their devices are asked to improve the process without having the keys or knowledge to do so.

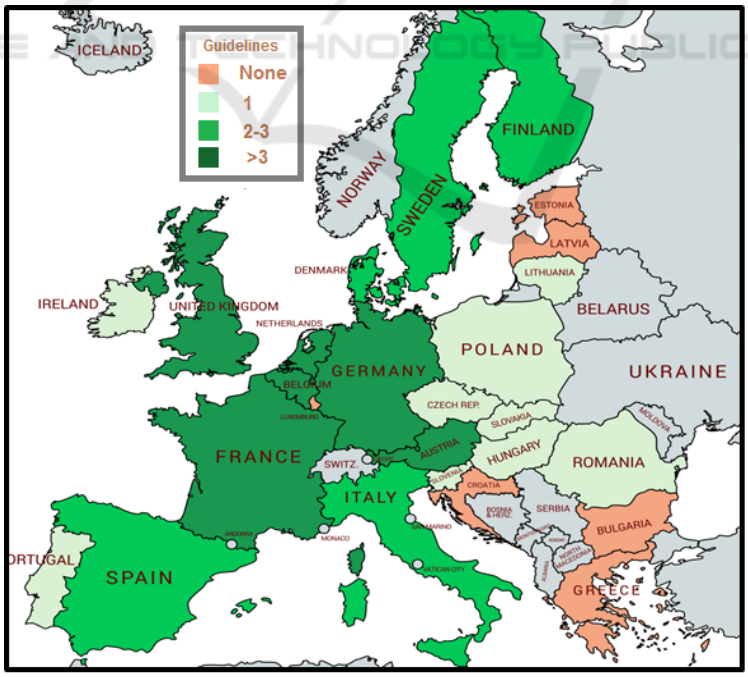

Figure 3: Number of guidelines on clinical evaluation of medical device per member state (Brunotte 2020).

3.4 Heterogeneity of Advice in the European Member States

In addition, broadly speaking, the MDRs leave the organization of clinical investigation protocol assessment and applicable authorization procedures to the discretion of the Member States. Different guidelines have been developed by member states (figure 3, from Brunotte, 2020) but standard methodologies are lacking. Those who should be doing clinical studies on HRMDs -first of all, manufacturers- have little visibility on what should be done as well as lacking the required resources and time.

Notified bodies must then request expert advice to scrutinize manufacturers' clinical evaluation assessment report on HRMDs. Expert opinion does not ensure a high level of clinical evidence and does not guarantee a high level of reproducibility.

3.5 Regulation Is Uniform Disregards Technological Characteristics and the Evolution of the Devices

The same clinical evaluation requirements apply to an English stick, a wheel chair, a hip prosthesis or a connected pacemaker. Passive prostheses and active implantable medical devices cover a large range of medical applications and patient needs. These two groups of HRMD exemplify very different R&D situations.

R&D of passive prostheses, for example, mainly involves the study of cells, their components, complex tissues and organs and their interactions with natural and synthetic materials. R&D of implanted passive prosthetic devices also involves developing and characterizing the materials used to measure, restore, and improve physiological functioning. These devices include coated stents, bio-valves, joint replacements and cellular bone grafts.

A second group is composed of active implantable medical devices (AIMDs), (European directive 90/385/EEC), mostly manufactured by large international companies with considerable technological resources (such as St Jude, Medtronic and Becton Dickinson). AIMDs cover many different clinical applications such as implantable defibrillators, neuromuscular stimulators, neuromodulators, cochlear implants and gastro-intestinal pacemakers. One of the best-known AIMDs is the cardiac pacemaker, introduced over 40 years ago, to deliver a controlled, rhythmic electrical stimulus to cardiac tissue. AIMDs have shown an impressive evolution over the last 20 years, not only in size and weight (which has been reduced by a factor of 10) but also in reliability, power consumption and physiological functionality. Specific recommendations have been issued from learned societies of cardiology.

New advances in this type of devices are expected with embedded algorithms of increasing complexity, including adaptive stimulation scenarios, diagnostic functions, data collection and transmission, as well as remote multiprogramming through a wireless link. Telemedicine may then facilitate diagnosis and care over distances and remote patient monitoring may lead to better home care e.g. a pacemaker implanted in a patient, the patient goes home, and the doctor monitors from a distance. Patients may also access health information via web portals, accessible anytime, anywhere. Consequently, the traditional healthcare model of patients traveling to see their doctor and being diagnosed and treated inside hospital walls is no longer the only relevant model.

The MDR does not differentiate between these different types of devices, despite their different characteristics and history of development

3.6 The Lack of Consideration of the Characteristics of HRMDs for Their Clinical Evaluation

Similar to drug evaluation, regulators around the world generally prefer evidence from RCTs when deciding whether to authorize the marketing of new medical devices. However, RCTs are time consuming and require significant financial resources which are often underestimated; this is particularly dangerous for SMEs with fragile economic statuses Above all, this type of trials of medical devices are difficult to perform for a number of reasons**:**

- a device implementation is a complex intervention and the outcomes of the intervention are generated by the combination of varied factors involved – e.g. the device, the clinicians implementing it, the training, the clinical condition of the patient receiving it, …
- the absence of comparators available on the market
- the device often evolves during the clinical trial due to direct feedback from first end-users,
- the difficulty of randomization due to the small sample size of the target population,

- the operator (surgeon, cardiologist, radiologist …) cannot be blinded to the type of device implanted, and no placebo exists except for devices that can be switched on and off remotely, but "sham operations" are almost never ethical because the patient experiences the risk of the intervention but no benefit.

Overall, clinical studies on medical devices are therefore far from systematic to run, and when carried out, they do not present the level of excellence (RCTs) expected by regulators to judge clinical evidence. But is this requirement for level of evidence really justified for all types of medical devices?

3.7 New Digital Health Developments Have Not yet Been Anticipated in MDR

Nowadays, **m-Health** (mobile health) apps are further widening the scope of how health services can be delivered and, more importantly, these technological advances are challenging traditional healthcare services. The vision that emerges from this is a health continuum (from healthy individuals to seriously ill patients), and to cope in the continuum of our lives we need Connected Health. The Connected Health paradigm covers that continuum and includes healthy individuals, those at risk and chronically ill patients. In Connected Health, individuals are equal partners with the healthcare professionals and take part in managing their own health.

p-Health (personalized health) and m-Health represent these new domains of application for information technology in the field of healthcare. Over the next decade it will be a huge challenge to propose new services to citizens and the right regulation. These technologies produce data from real-world settings. In addition to regulations, in particular with the General Data Protection Regulation (GDPR), the production and analysis with AI of big data is actively studied in order to develop new knowledge that has so far been unaffordable.

3.8 High-risk Concept Poorly Conceived in the MDR

Only three quotations of the word "high-risk" appear in the 175 pages of the MDR, without any definition.

The clinical evaluation and assessment of level of risk should incorporate all risk factors in the use of HRMD and human factor issues.

4 OPPORTUNITIES FOR CLINICAL INVESTIGATION DESIGN

The European Commission has launched many calls for projects on computer modeling, usability methods, real world data processing and innovative medical devices. Some of these will be useful for the future.

Progress in computer modeling and simulation applied to disease management is a European strength and various Decision Support Systems have been developed for different medical disciplines. Through its new initiatives on digital health and care within the Digital Single Market policy, the European Commission aims to leverage the potential of big data and high-performance computing for the emergence of new personalized prevention methods and treatments.

The economic aspects will be addressed in existing European initiatives on the subject (e.g. TBMED, MedTechHTA, Impact-HTA projects).

4.1 New Methodological Pathway for Clinical Studies on HRMDs

The most important factor for successful marketing approval, practitioner adoption, and safe use of higher-risk medical devices is robust clinical evidence.

In the United States, computer modeling and simulation (i.e., *in silico* methods) are gaining more and more recognition from regulatory boards for the evaluation of the safety and performance of medical devices. For example, from 2002 to 2019 in the USA, at least 21% of the 565 pre-market approval (PMA) applications for HRMDs had computational modeling efforts provided in the Summary of Safety and Effectiveness Data (Morrison 2018, 2019). For the past few years, the FDA has been accepting regulatory files including digital models, adaptive studies, hybrid trials, real-world data and experience. The FDA has thus developed numerous general guides on these subjects to help medical device manufacturers carry out adequate studies to obtain their product launches (FDA 2010, 2018, 2020).

Given the shortcomings of the MEDDEV and MDCG guidelines and of the ISO/FDIS 14155

standards in terms of the expected clinical study design, further issues concern the following considerations:

- alternatives to classical randomized controlled trials, including pragmatic trials and adaptive design
- alternatives to frequentist approaches
- integration of Human Factors and usability study methods
- the place of computer modelling and simulation models (*in silico models and trials*)
- the use of real-world data with *new analytical capabilities* and mathematical models.
- a deal with companies to get real world data (RWD) generated by HRMD against freely use of academic simulation models

4.2 Adaptive Methodologies and Pragmatic Trials Have Been Developed as an Alternative to the Classical 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 but have remained unused for many years especially by the European notified bodies for MDs evaluation.

Methodologists propose using tracker design trials (Lilford 2000), sequential trials (Hamilton 2012), 'Multi-Arm Multi-Stage' trials (Wason 2014, Wathen 2017), pragmatic trial **(**Ford 2016, Loudon 2015, Thorpe 2009, Simon 2019, Gamerman 2019) and adaptive trials (Simon 2013, Meurer 2016, Magirr 2016, Lai 2019) 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). These trials rely on planned interim analyses which allow the investigator to glean useful information for adapting the strategy. They are particularly relevant to the context of HRMD clinical evaluation.

With adaptive methods it is also possible to strengthen the clinical evaluation of medical devices by authorizing the analysis of multiple 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. With these methods it is also possible to combine the early exploratory phases with the demonstrative phases which may help to accelerate and optimize the development and implementation of innovative devices. When certain centers only use one of the two techniques under study and do not know the other technique, or only master 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, Barker 2016) to increase the participation of doctors and the reliability of the evaluation. When one arm in the study is less attractive than the other, studies may be carried out according to a Zelen plan (Zelen 1990) or according to a complete cohort pattern. These types of trials introduce flexibility in the attribution of treatments and allow better acceptability of the randomization by the patients and also give us the possibility of adjusting the results to the randomization. Group sequential design and adaptive sample-size adjustment are often used to make study durations shorter and include a smaller number of subjects.

Nevertheless, there has been criticism of these adaptive designs and it will be important to analyze the biases and added value of these proposals, their acceptability by the stakeholders and their admissibility by the European authorities.

For the past few years, the FDA has been accepting regulatory files including digital models, adaptive studies, hybrid trials design, real-world data and experience (Guetterman 2017, Campbell 2019). FDA has thus developed numerous guides on these subjects to help manufacturers of medical devices to carry out adequate studies to obtain a marketing of their products (FDA 2010, 2018, 2020).

4.3 Bayesian Approaches May be used to Implement and Analyze Clinical Trials

Bayesian approaches give the possibility of combining prior information before the trial (previous studies, expert opinion, literature…) and current information during the trial to formulate or reformulate decision-making rules (Campbell 2011, Ribouleau 2011, Wei 2018).

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 (Pennello 2008). There are no statistical tests but the probability of the treatment under experimentation being effective has a 95% credibility threshold. However, it is very important that the *a priori*

information used does not over influence the final result (sensitivity analysis required). The quality of information supplied a priori is therefore a key element in the credibility of results.

4.4 Human Factors Engineering

There are a variety of human factors and usability evaluation methods (Genise, 2002) for all stages of design and development, from product definition to final design modifications like cognitive modeling methods, inspection methods, inquiry methods, prototyping methods, usability testing etc. Certain methods use data from users, while others rely on usability experts. When choosing a method, cost, duration and appropriateness should be considered.

4.5 In Silico Modelling

The beginning of the 21st century saw the birth of a completely new way to investigate living organisms through computer simulations, called in silico medicine. Over the last 15 years, significant efforts have been made to build numerical patient models from multimodal images, for instance, for surgical planning and image-guided surgery.

Initially released in 2007, the Virtual Family (https://www.fda.gov/about-fda/cdrh-offices/virtual-family) is a set of four highly detailed, anatomically correct whole-body models of an adult male, an adult female, and two children. The Virtual Family project was carried out in collaboration between the FDA and academic or private European partners from Erlangen, Germany, and Zürich, Switzerland. Currently, the Virtual Family models are used for electromagnetic, thermal, acoustic, and computational fluid dynamics simulations. Examples of applications of electromagnetic and thermal simulations are the assessment of the safety of active and passive medical implants in a Magnetic Resonance Imaging (MRI) environment and the evaluation of the safety and efficacy of ablation devices. Since the end of 2014, the Virtual Family has been regularly used in medical device submissions to the FDA.

The *Virtual Physiological Human* (VPH) is an initiative developed over the last decade and supported by the European Commission to create a computational framework designed to facilitate the understanding of the integrative function of molecules, cells, tissues, and organs and, by this, to construct a multiscale *in silico* model of the human physiology (Viceconti 2008). The collective framework will make it possible to share resources and observations formed by institutions and organizations, creating disparate but integrated computer models of the mechanical, physical and biochemical functions of a living human body. VPH is a framework which aims to be descriptive, integrative and predictive. The framework consists of large collections of anatomical, physiological, and pathological data stored in digital format, with predictive simulations developed from these collections and services intended to support researchers in the creation and maintenance of these models, and also the creation of end-user technologies to be used in clinical practice.

The validation of in silico clinical trial models poses relevant theoretical problems. However, these have been discussed in specialized publications (Coveney, 2014) and a standardization committee (ASME V&V-40 verification and validation in computational modelling of medical devices), which worked on some codified guidelines (Popelar, 2013). A key aspect, which was promoted within the Medical Device Innovation Consortium (Kampfrath 2013), but that emerged again and again during the Avicenna consensus process, is that of model credibility. The process to ensure that a predictive model is indeed accurate in its predictions is somehow at the center of a paradox. Models are usually developed to predict things that cannot be easily measured, so how do we know how accurate these predictions are?

4.6 Use of Real-World Data

The use of computers, mobile devices, wearables and other biosensors gathering huge amount of health data has been rapidly accelerating. These data hold potential to allow us to better design and conduct clinical trials and studies in the healthcare setting to answer questions previously thought infeasible. In addition, with the development of sophisticated, new analytical capabilities, we are able to better analyze these data (Kumsa 2018, Sherman 2016).

The increasing availability of data generated by such devices poses challenges regarding management and data workflows. The use of artificial intelligence algorithms in medical devices, can lead to undetermined risks for users, and require a proper framework for development and validation. Progress, particularly in computing and AI, data and wearable accessibility, is often made at a much faster rate than guidelines and recommendations are issued.

5 CONCLUSIONS

In summary, investigation protocols of high risks medical devices, advised and authorized by the National competent authorities in Europe, are few and heterogenous. There is a lack of quality in the existing studies, a lack of methodological knowledge and consequently high expectations for assistance from those involved in the design of clinical study protocols on HRMD. Guidance that is specific to the different type of devices is missing.

The “new” EU MDR 2017/745 coming into effect in May 2021, by obliging clinical investigation and post-market follow-up, offers the opportunity to develop novel pathways for the clinical development of HRMDs. In particular, there is a perceived lack of knowledge and training in clinical trial skills in European medical device companies who could greatly benefit from a clarification of expectations linked to the MDR for HRMDs..

Nevertheless, the available guidelines (from EU directives, MDCG new guides or national transcriptions) remain vague and imprecise, also many companies are leaving Europe due to the complexity and imprecision of MDR. They move to the US where the regulatory pathway is clearer & faster.

The risks of this situation in Europe are reinforced by many threats:

- the current observation on the lack of quality clinical studies,
- the specificities of HRMD by medical speciality,
- the economic fragility of European HRMD companies (95% SMEs),
- the high expectations of safety on the part of patients and healthcare professionals,
- the loss of attractiveness of Europe for carrying out clinical studies,
- the desire for a "smooth transition" from directives to MDR without real means.,
- the attribution of a CE marking by various private structures,
- the diversity of approach from one notified body to another, and the absence of a centralized procedure

At both European and national level, before and after marketing, a new balance needs to be found between the need for rigorous evidence and the real world complexity of gathering such evidence; a balance between strict regulation and high levels of evidence for high risk medical devices, and the possibility of other types of evidence for devices associated to lower levels of risk.

Adaptive designs, pragmatic trial, usability methods, computer modeling and real world data are gaining more and more traction in the United States for assessing the safety and performance of medical devices from a regulatory view- point. The European Commission has launched many calls for projects on these subjects, generating new knowledge and new teams of experts. Expectations from stakeholders of clinical investigations tend to bring these experts and knowledge together to prioritize the methods and develop useful guidelines for those who wish to set up clinical studies on HRMDs.

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