



**HAL**  
open science

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

L. Pazart, S. Pelayo, Thierry Chevallier, G. Gruionu, P. Mabo, Y. Bayon, F. Barbot, T. Lihoreau, C. Roussel, N. Maglaveras, et al.

## ► To cite this version:

L. Pazart, S. Pelayo, Thierry Chevallier, G. Gruionu, P. Mabo, et al.. Threats and Opportunities for the Clinical Investigation of High-risk Medical Devices in the Context of the New European Regulations. 14th International Joint Conference on Biomedical Engineering Systems and Technologies - BIOSTEC 2021. Special Session on Dealing with the Change in European Regulations for Medical Devices, Feb 2021, Vienna, Austria. pp.274-284, 10.5220/0010382902740284 . hal-03657023

**HAL Id: hal-03657023**

**<https://hal.science/hal-03657023v1>**

Submitted on 9 May 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

# THREATS AND OPPORTUNITIES FOR THE CLINICAL INVESTIGATION OF HIGH-RISK MEDICAL DEVICES IN THE CONTEXT OF THE NEW EUROPEAN REGULATIONS

Pazart L<sup>1,2</sup>, Pelayo S<sup>1,3</sup>, Chevallier T<sup>1,4</sup>, Gruionu G<sup>5,6</sup>, Mabo P<sup>1,7</sup>, Bayon Y<sup>8</sup>, Barbot F<sup>1,9</sup>, Lihoreau T<sup>1,2</sup>, Roussel C<sup>1,10</sup>, Maglaveras N<sup>11</sup>, Lekka E<sup>11</sup>, Ferreira HA<sup>12</sup>, Rocha I<sup>13</sup>, Geris L<sup>14</sup>, Lavet C<sup>1</sup>, and the EVAL-HRMD project consortium

<sup>1</sup>Inserm, Tech4Health, FCRIN F-31000 Toulouse, France

<sup>2</sup>Univ. Franche-Comté, Inserm CIC1431, CHU Besançon, F-25000 Besançon, France

<sup>3</sup>Univ. Lille, Inserm, CHU Lille, ULR 2694 – METRICS, F-59000 Lille, France

<sup>4</sup>IDIL- Nimes University Hospital and INSERM IDESP- F-30000- Nimes, France

<sup>5</sup>Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, IN 46202, USA.

<sup>6</sup>INCESA Institute, Faculty of Mechanics, University of Craiova, Craiova 200512, Romania.

<sup>7</sup>Univ Rennes, CHU de Rennes, Rennes, France

<sup>8</sup>Medtronic – Sofradim Production, Trévoux France

<sup>9</sup>CIC 1429 Inserm, Hôpital Raymond Poincaré APHP, Garches France

<sup>10</sup>CIC 1415, CHU Tours, Inserm, University of Tours, France

<sup>11</sup>Lab of Medical Informatics, Aristotle University of Thessaloniki, Thessaloniki, Greece

<sup>12</sup>Instituto de Biofísica e Engenharia Biomédica, Faculdade de Ciências da Universidade de Lisboa, Portugal

<sup>13</sup>Lisbon School of Medicine & Cardiovascular Centre, Universidade de Lisboa, Lisboa, Portugal

<sup>14</sup>Biomechanics Research Unit, GIGA In Silico Medicine, University of Liège, Belgium

**Keywords:** High-risk Medical Device, Medical Device Regulation, Clinical Investigation, EU MDR 2017/745, regulatory science.

**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.

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.

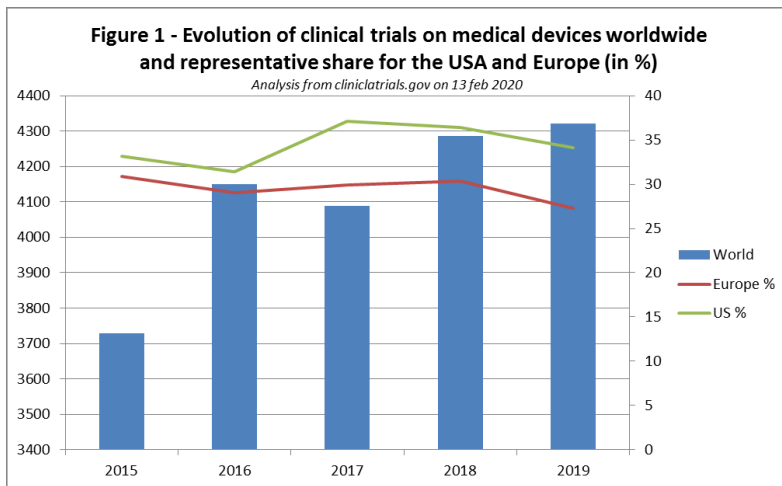
Although these issues are taken into account in usability standards (IEC 62366-1 and IEC 60601-1-6) and many methods of Human Factor Engineering (HFE) have existed for years, they seem to be underused (BSI 2016).

## 3. THREATS ARISING FROM THE CURRENT SITUATION IN EUROPE

### 3.1 The loss of Europe's attractiveness for carrying out clinical studies

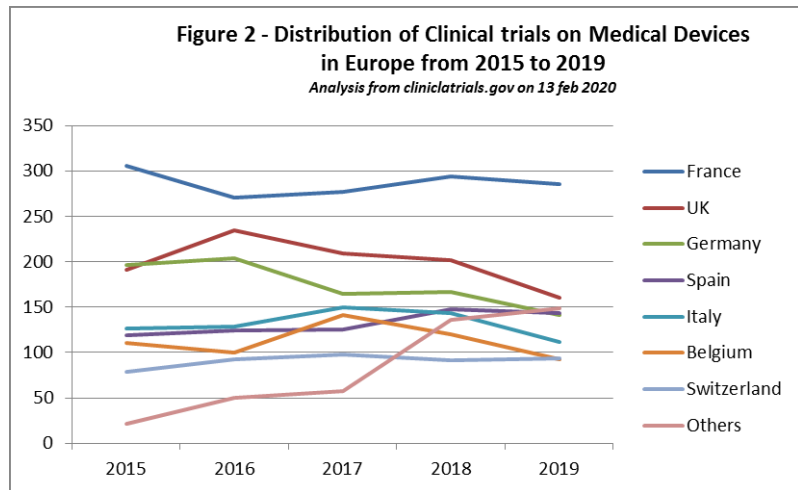
The complexity of the regulatory process for HRMDs is partly due to a significant fragmentation of the global market. Namely, many countries have their own set of rules around the world (Thompson, 2012). A new device classified into Class III in Europe may very well be considered a Class II device according 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](http://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%).



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.

### 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.

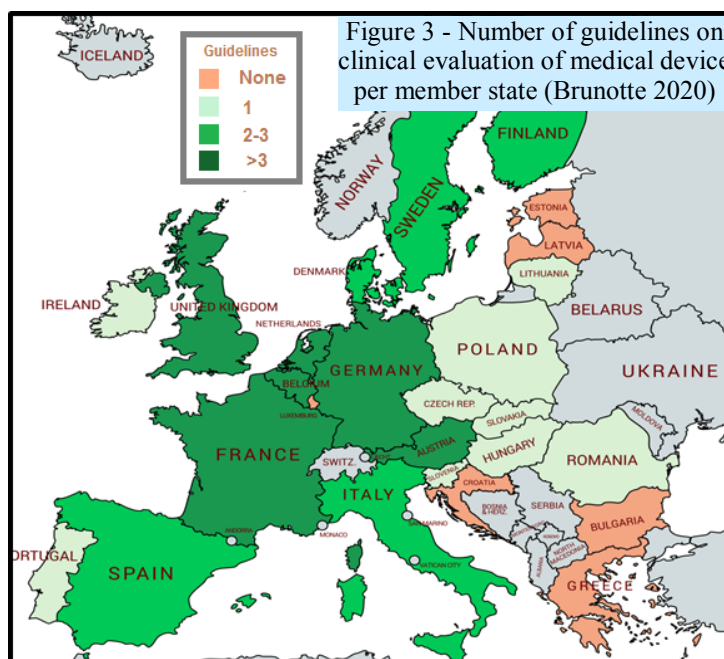


Figure 3 - Number of guidelines on clinical evaluation of medical device per member state (Brunotte 2020)

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 gastrointestinal 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, Gaman 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 inefficacy, 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.

## **4 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.

## **ACKNOWLEDGEMENTS**

We would like to thank all those who contributed to the preparation of the Eval-HRMD project, and especially Joanna Baranowska, Marine Beaumont, Regis Beuscart, Patrick Boisseau, Gaelle Brunotte, Guy Carrault, Jacques Demotes, Marlene

Durand, Maria Dutarte, Jérôme Fabiano, Jacques Feblinger, Joris Giai, Lucian Gruionu, Gemma Killeen, Amélie Michon, Alexandre Moreau-Gaudry, Claire Nassiet, Frédéric Patat, Pierre Pautre, David Orlikowski, Delphine Smagghe, Dimitar Tcharaktchiev, Chrystelle Vidal, Sebastian Wawrocki. The project received a grant from the National Research Agency to support the networking of partners.

## REFERENCES

- ASME - American Society of Mechanical Engineers - standard V&V40 2018: "Assessing credibility of computational models through verification and validation: application to medical devices"
- Barker, D, et al., 2016. Stepped wedge cluster randomised trials: a review of the statistical methodology used and available. *BMC Med Res Methodol* 6 ;16:6..
- British Standards Institution (BSI), 2016 The growing role of human factors and usability engineering for medical devices, white paper.
- Brunotte G., Beuscart, R., Pariset, A. Pazart, L. 2020 Place of High-risk Medical Devices in European Recommendations with a Focus on End-users. In Proceedings of the 13th International Joint Conference on Biomedical Engineering Systems and Technologies - Vol 1: BIODEVICES, p 350-360
- Campbell, G, 2011. Bayesian statistics in medical devices: innovation sparked by the FDA. *J Biopharm Stat.* 21:871-87.
- Campbell B, Wilkinson J, Marlow M, et al. 2019 Generating evidence for new high-risk medical devices. *BMJ Surg Interv Health Technologies*;1:e000022
- Coveney, P., Diaz, V., Hunter, P., Viceconti, M., Eds., 2014. *Computational Biomedicine*. Oxford, Oxford University Press.
- FDA - Guidance for the use of Bayesian Statistics in Medical Device Clinical Trials; Guidance for industry and FDA Staff on February 5, 2010.
- FDA - Guidance on the use of "real-world evidence" — healthcare information from atypical sources, including electronic health records, billing databases, and product and disease registries — to assess the safety and effectiveness of drugs and devices. 2018
- FDA - Adaptive Designs for Medical Device Clinical Studies, Guidance for Industry and Food and Drug Administration Staff, Document issued on July 27, 2016, new version 2020 under comments.
- Ford I, Norrie J. 2016 Pragmatic Trials *N Engl J Med* 2016; 375:454-463 DOI: 10.1056/NEJMra1510059
- Gameran, V., Cai, T. & Elsäßer, (2019) A. Pragmatic randomized clinical trials: best practices and statistical guidance. *Health Serv Outcomes Res Method* 19, 23–35. doi.org/10.1007/s10742-018-0192-5
- Genise P. 2002 "Usability Evaluation: Methods and Techniques: Version 2.0" August 28,. University of Texas.
- Guetterman, TC, et al. 2017. The life cycles of six multi-center adaptive clinical trials focused on neurological emergencies developed for the Advancing Regulatory Science initiative of the National Institutes of Health and US Food and Drug Administration: Case studies from the Adaptive Designs Accelerating Promising Treatments Into Trials Project. SAGE Open Med..
- Guideline on clinical Trials in small populations; Committee for medicinal products for human use on 27 July 2006.
- Hamilton, C,et al., 2012. Sequential design for clinical trials evaluating a prosthetic heart valve. *Ann Thorac Surg*, 93(4): 1162-1166.
- HAS, Methodological choices for the clinical development of medical devices; HAS evaluation report dated October 4th, 2013.
- HAS, 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.
- Kampfrath, T., Cotten, S. W., 2013. The new collaborative path in medical device development: The medical device innovation consortium. *Clinical Biochemistry* 46, 1320-1322
- Kumsa , Doe, et al. (2018) "Public regulatory databases as a source of insight for neuromodulation devices stimulation parameters ." *Neuromodulation : Technology at the Neural Interface* 21. 2: 117- 125 .
- Lai, TL, et al., 2019. Adaptive enrichment designs for confirmatory trials. *Stat Med* 38 (4) :613-624.
- Lilford, R, et al., 2000. Trials and fast changing technologies: the case for tracker studies. *BMJ*, 320 (7226): 43–46.
- Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M et al. 2015 The PRECIS-2 tool: designing trials that are fit for purpose *BMJ*; 350 :h2147
- Magirr, D, et al., 2016. Sample Size Reassessment and Hypothesis Testing in Adaptive Survival Trials. *PLoS One*. 11(2):e0146465.
- Meurer, WJ, et al., 2016. Attitudes and opinions regarding confirmatory adaptive clinical trials: a mixed methods analysis from the Adaptive Designs Accelerating Promising Trials into Treatments (ADAPT-IT) project. *Trials*. 29;17:373.
- [MDCG 2019-9 Summary of safety and clinical performance A guide for manufacturers and notified bodies - August 2019](#)
- [MDCG 2020-1 Guidance on Clinical Evaluation \(MDR\) / Performance Evaluation \(IVDR\) of Medical Device Software](#)
- [MDCG 2020-5 Clinical Evaluation - Equivalence. A guide for manufacturers and notified bodies](#)
- [MDCG 2020-6 Regulation \(EU\) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC. A guide for manufacturers and notified bodies](#)
- [MDCG 2020-7 Post-market clinical follow-up \(PMCF\) Plan Template. A guide for manufacturers and notified bodies](#)

[MDCG 2020-8 Post-market clinical follow-up \(PMCF\) Evaluation Report Template. A guide for manufacturers and notified bodies](#)

Morrison, Tina (2019): LyoHUB: Advancing Regulatory Science with Modeling and Simulation at the FDA. figshare. Presentation.

<https://doi.org/10.6084/m9.figshare.9910832.v1>

Morrison, T. M., et al. , (2018 ). Advancing regulatory science with computational modeling for medical devices at the FDA's Office of Science and Engineering Laboratories . *Frontiers in medicine* , 5 .

Olberg B, Fuchs S, Panteli D, Perleth M, Busse R. 2017 Scientific Evidence in Health Technology Assessment Reports: An In-Depth Analysis of European Assessments on High-Risk Medical Devices. *Value Health*. Dec;20(10):1420-1426.

Pennello, G, et al., 2008. Experience with reviewing Bayesian medical device trials. *J Biopharm Stat* 18 :81-115.

Popelar, C. F., 2013. Verification & Validation in Computational Modeling of Medical Devices (V&V-40): ASME subcommittee and guide. FDA/NIH/NSF Workshop on Computer Models and Validation for Medical Devices. Silver Spring, MD.

Ribouleau, L, et al., 2011. Bayesian statistical method was underused despite its advantages in the assessment of implantable medical devices. *J Clin Epidemiol*. 64:270-9.

Sauerland S, Fujita-Rohwerder N, Zens Y, Molnar S. Premarket evaluation of medical devices: a cross-sectional analysis of clinical studies submitted to a German ethics committee. *BMJ Open*. 2019 Feb;9(2):e027041. DOI: 10.1136/bmjopen-2018-027041.

Sherman RE & al. (2016) Real-World Evidence — What Is It and What Can It Tell Us? *N Engl J Med* 2016; 375:2293-2297 DOI: 10.1056/NEJMs1609216

Simon, N, et al., 2013. Adaptive enrichment designs for clinical trials. *Biostatistics* 14(4):613-25.

Simon, G.E., Shortreed, S.M., Rossom, R.C. et al. (2019) Principles and procedures for data and safety monitoring in pragmatic clinical trials. *Trials* 20, 690. doi.org/10.1186/s13063-019-3869-3

Thorpe KE, Zwarenstein M, Oxman AD, et al. 2009 A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol*.;62(5):464-475. doi:10.1016/j.jclinepi.2008.12.011

Viceconti M, Clapworthy G, Van Sint Jan S. 2008 The Virtual Physiological Human - a European initiative for in silico human modelling - . *J Physiol Sci*. Dec;58(7):441-6.

Wason JM, et al., 2014. A comparison of Bayesian adaptive randomization and multi-stage designs for multi-arm clinical trials. *Stat Med*. 33 (13):2206-21.

Wathen JK et al., 2017. A simulation study of outcome adaptive randomization in multi-arm clinical trials. *Clin Trials* 14 (5):432-440.

Wei, B, et al., 2018. A Bayesian analysis of small n sequential multiple assignment randomized trials (snSMARTs). *Stat Med* 20 ; 37 (26) :3723-3732.

WHO, 2019. Medical devices URL (accessed 12.18.19).[http://www.who.int/medical\\_devices/en/](http://www.who.int/medical_devices/en/)

World Health Organization (2014) WHO handbook for guideline development, 2nd ed. World Health Organization. 167 pages <https://apps.who.int/iris/handle/10665/145714>

Zelen, M, et al., 1990. Randomized consent designs for clinical trials: an update. *Stat Med* 9 (6): 645-56