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Clinical research challenges in the era of cardiovascular medical devices

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Abstract

New therapeutic alternatives, such as innovative medical devices, are frequently the only treatment options left for patients when other efficient medical modalities are lacking or insufficient. Development of novel devices, which are safe and effective, requires understanding of complex premarket and postmarket provisions, including characteristics of clinical trials. Speeding up patient access to new technologies may imply the need to make choices in terms of extent and robustness of clinical evaluation without losing the patient safety perspective. In such situations, some challenges can readily arise due to existing methodological solutions and aspects of current legislation in the field. In this context, some challenges, occurring at various stages of the device lifecycle, will be presented in order to observe the changes and hopefully to contribute to better knowledge and improvements in the area.

Key words: medical device, clinical research, legislation, challenges.

Streszczenie

Nowe rozwiązania terapeutyczne, takie jak innowacyjne wyroby medyczne, są często jedyną możliwością leczenia pacjentów, gdy nie ma innych efektywnych metod lub są one niewystarczające. Rozwój nowatorskich wyrobów – bezpiecznych i efektywnych – oznacza potrzebę zrozumienia złożonych warunków przed- i porynkowych, włącznie z charakterystyką badań klinicznych. Przyspieszenie dostępu pacjenta do nowych technologii może wymagać dokonania wyborów dotyczących zakresu i rzetelności oceny klinicznej bez utraty perspektywy bezpieczeństwa pacjenta. W takiej sytuacji mogą się pojawić pewne wyzwania, wynikające z istniejących rozwiązań metodologicznych i obecnego prawodawstwa. W tym kontekście zostaną przedstawione niektóre wyzwania występujące na różnych etapach cyklu życiowego wyrobów medycznych w celu zwrócenia uwagi na zachodzące zmiany oraz w nadziei, że przyczyni się to do wzrostu wiedzy i poprawy sytuacji w tym zakresie.

Słowa kluczowe: wyroby medyczne, badania kliniczne, przepisy prawne, wyzwania.

Introduction

There is a growing problem regarding medical research due to the decreasing supply of adequately educated researchers as well as changes in funding policies for institutions of higher learning, medical schools and universities [1]. In an article published on the Nature website on June 4th 2014, Cressey estimated that the decline in clinical trials in the European Community (EC) has been 25% over the last 4-year period. This is not good at all. The number of researchers who are clinically active has decreased, and so has the number of clinical investigations and medical doctoral dissertations, and at the same time we have an unprecedented need for more medical research due to several factors. These include the continuing tremendous progress in medical science and medical technology in general and the ever increasing amount of medical devices in particular, the ageing population, and the cumulative economic burden on the health sector.

Medical devices

There are many medical devices on the European market, some 500 000 different ones, ranging from simple products such as dressing plasters to complex circulatory assist machines and sophisticated proton radiation therapy units. Nowadays medical devices are a more and more important part of not only highly specialized hospital care but even primary care, ambulatory and home care. Obviously annual costs are also growing quickly, and in Sweden it is estimated that as much as 3 billion SEK is spent on devices annually (~300 million Euro). Cardiovascular (CV) devices represent one of the dominant segments. The majority of CV devices are class III devices. All devices are categorized into 4 classes (class I, IIa, IIb, III) according to the risk they pose during their usage. Class 3 is the highest risk class. Devices differ also in terms of quantity and quality of clinical evidence needed to be documented as well as the

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necessity for conformity assessment from a Notified Body (NB), which is an independent, accredited body entitled by a Member State's accrediting authority. Manufacturers are obliged to obtain NB certification for their quality and risk management systems, but finally it is always the manufacturer that places the CE mark on the product, thus taking all responsibility for its clinical performance and safety. The reason why many CV devices belong to class III is that the majority of them have such features as structural complexity, multiple components design, and even diverse intricate functional interfaces. All of these make them prone to failures, which evidently have a strong impact on both their safety and performance. Device failures imply significant risks for the patients and frequently even for users such as medical professionals, elderly home personnel and others who apply them. So on one hand they can have undesirable side effects leading to complications, while on the other they usually are very efficient and sometimes can be the only available methods for the treatment of high-risk patients. How high should the acceptable risks be and how efficient should the devices be? What procedures have to be applied to ensure that legal requirements of safety and efficacy are fulfilled? The estimations can be rather subjective, and making a choice is not easy. The conceptual work leading to introduction of novel device-based therapies is different than in the case of drugs because of the frequently short lifecycle of devices with a high rate of technology change with a continuum of incremental design alterations, problems with evaluations due to difficulties to perform controlled randomized studies, issues of equivalence, high possibility to visualize performance, strong influence of the learning curve, and complexity of the legislative framework. One of the potent solutions, how to cope with this challenge, is the proper legislation and strict adherence to it by all the parties involved in the development of the medical devices [2].

Clinicians and medical devices

Many clinicians are directly or indirectly involved in the parts of the process of development of the new medical devices – some of them as inventors, some as authors of clinical evaluation reports (CEVR) or investigators in clinical investigations (CI), and the majority as potential users of devices after their successful launching. Clinical trials are frequently necessary to acquire sufficient clinical data supporting clinical claims and validating safety of the medical products before a manufacturer can CE mark the product. The CE marking on a product is a manufacturer's declaration that the product complies with the essential requirements of the relevant European health and patients safety legislation, allowing the product to be legally placed on the market, ensuring the free movement of the product within the EC and permitting withdrawal of non-conforming devices by competent authorities (CA) and customs.

The key stakeholders, including device producers, politicians, academia, clinical experts, CA, and health care professionals, are in need of well-functioning communication to maintain an optimal level of patient safety and device efficacy weighted against patients' and caring doctors' wishes of prompt access to the novel devices.

Physicians involved in clinical trials, which in essence are aimed at generating clinical evidence, may be unaware of the device risks or unprepared for optimal assessment of the undue risks associated with innovative devices. It makes the evidence of collected data unreliable, and when the sponsor of the trial considers every applicable measure to accelerate the process of putting the device on the market, the consequence can be generation of highly uncertain risk/benefit estimation [3]. However, the average clinician's knowledge of the regulatory framework with regard to the medical devices is extremely low. This article will hopefully fill this gap and stimulate the researchers and those responsible for research policy to undertake deeper studies of issues taken up in the article.

Regulatory framework

The medical professionals participating in CI can meet different clinical and regulatory challenges and even the more or less conscious temptation to defiance with regard to new cardiovascular medical devices. Clinical ones are a matter confined to scientific frameworks of the specific area of research and are outside the scope of this paper. Regulatory ones are often derived from ignorance with regard to existing laws. Nevertheless, the regulatory challenges are very intimately associated with the clinical ones, so some of them will be presented here later, in a clear clinical setting. Regulatory problems can also depend on differences in legislatures, because there are different laws valid for different countries of the world. In this article, the challenges are presented from the European point of view, more precisely from the EC perspective. In the EC the main law considering medical devices is composed of three directives, and each of the 28 EC member states has to incorporate them in their national regulations: 93/42/EEC concerning medical devices (MDD), 90/385/EEC concerning active implantable medical devices (AIMDD), 98/79/EEC concerning *in vitro* diagnostic medical devices (IVD). All directives are available in various languages to download from the EC website: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:en:PDF.

The lifecycle of devices consists of several phases, which are or can be repeatable processes, and seems to be straightforward (Fig. 1). Looking at the simplified lifecycle scheme it is easy to understand that legislation involved is extensive and substantial because various regulations regarding technical, electrical, radiation protection, environmental aspects, etc. can be applicable. Apart from laws there can be norms and standards to consider. Rules governing the CE marking process originate from the abovementioned directives. The way to CE mark can be, in a simplistic manner, summarized as an 11-step procedure (Fig. 2).

It is worth noting that there is a clinical evaluation (CEV) obligation in all classes of devices. The mentioned "Declaration of Conformity" is a legally binding document written

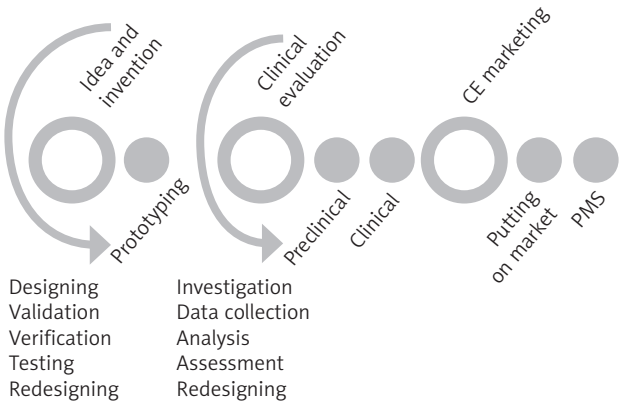

Fig. 1. Lifecycle of medical devices seen as a chain of events

Arrows – events which can be iterative, PMS – post-market surveillance

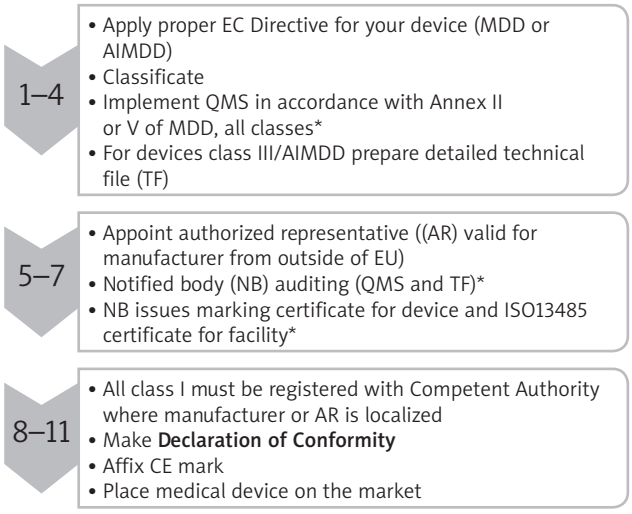

Fig. 2. Eleven steps on the medical device CE marking pathway

MDD – medical devices directive, AIMDD – active implantable medical devices directive, QMS – Quality Management System (usually ISO 13485), *except devices of Class I, which are neither sterile nor have measuring function

by the manufacturer stating that the medical device is in compliance with essential requirements of the applicable EC directive. This document has to include the following information: product identification, manufacturer identification, applicable directive, etc.

The regulatory obligations on the pathway to the CE mark for medical devices are clearly defined (Fig. 3). They are specified in different annexes of the appropriate directive. Additionally, there is a plethora of guidelines (called MEDDEV) which contain direct and efficient support for implementing the directives in a particular situation. They provide assistance in various fields, for instance when creating a clinical evaluation report, serious adverse event reporting, classification of medical devices, preparation of clinical investigation, making assessment of clinical investigation by CA, etc. As some procedures can be difficult, many companies engage qualified consultants from a contract research organization specializing in various stages and aspects of the development of the device. In contrast

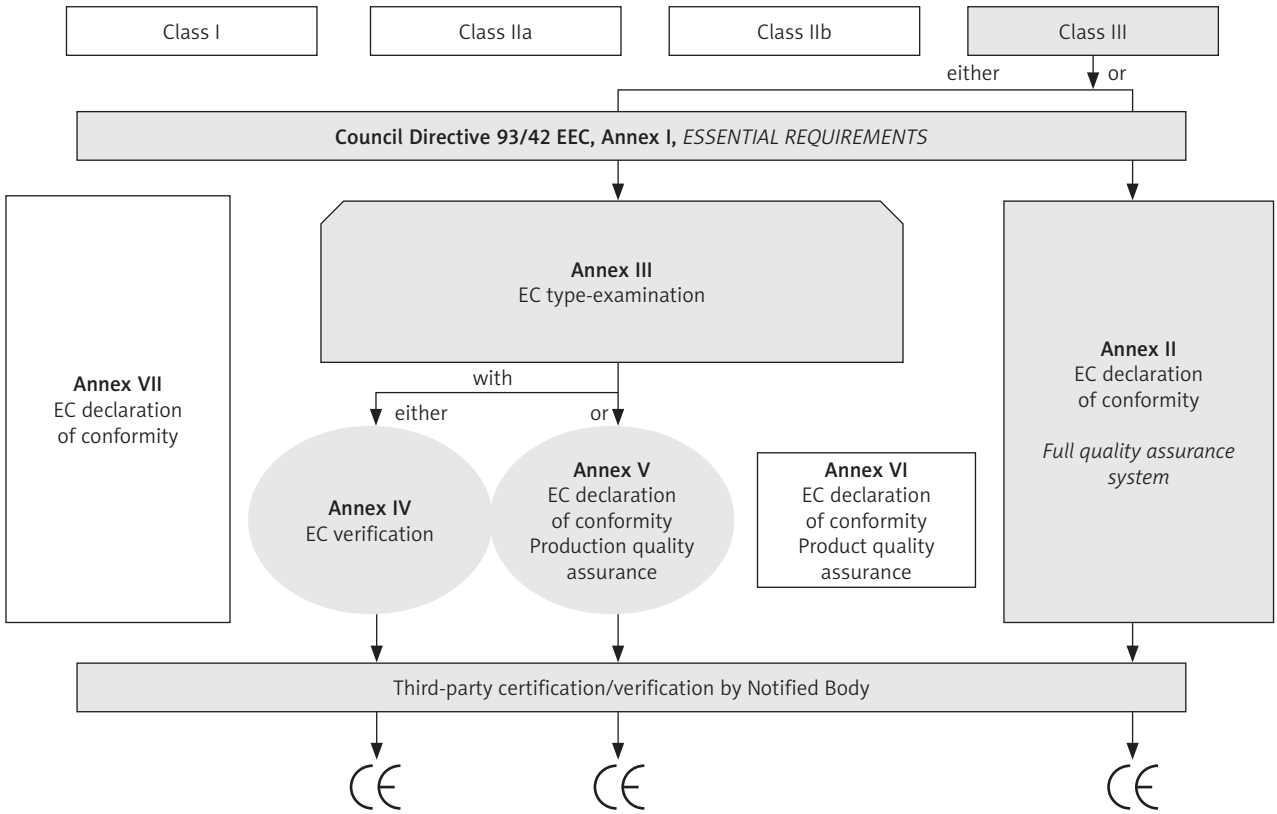

Fig. 3. Regulatory aspects of CE marking pathway for class III device. Modified with permission from P. Landvall "Medicintekniska produkter", 2010, SIS Förlag, Stockholm

to processes involved in development of new medicines where the CA in a member state is a clear partner in the medicine approval process, with regard to devices, the role of the CA is limited to supervision activities.

The term 'medical device' is not self-explanatory, so before addressing the issue of requirements for devices it is necessary to remember the definition of medical device according to EC law. 'Medical device' means "any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

– diagnosis, prevention, monitoring, treatment or alleviation of disease,
– diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
– investigation, replacement or modification of the anatomy or of a physiological process,
– control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means".

According to Annex 1 of MDD the general requirements are: "The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their intended use constitute acceptable risks when weighed against the benefits to the patient and are compatible with high level of protection of health and safety" [4]. Essential requirements cover various parts of efficacy and safety. Some aspects of design and manufacturing considered in the requirements are: *safety aspects including* chemical, physical and biological properties, infection and microbial contamination, manufacturing and environmental properties, protection against radiation, requirements for medical devices connected to or equipped with an energy source, protection against mechanical risks, protection against the risks posed to the patient by supplied energy or substances, protection against the risks posed to the patient for devices for self-testing or self-administration, information supplied by the manufacturer; and *performance aspects include* the following: the clinical claims have to be based on clinical evidence, intended indications as well as the population should be thoroughly described, and efficacy should be precisely specified and estimated. Finally, the most crucial thing is that the benefits offered by the medical device should clearly outweigh the residual risks associated with the usage of it.

MDD Annex I, in section 6a, imposes that demonstration of the conformity with the essential requirements must include a clinical evaluation (CEV) in accordance with Annex X, which in turn stipulates that "as a general rule, confirmation of conformity with the requirements concerning the characteristics and performances referred to in Sections 1 and 3 of Annex I, under the normal conditions of use of the device, and the evaluation of the side-effects and of the acceptability of the benefit/risk ratio referred to in Section 6 of Annex I, must be based on clinical data. The evaluation of this data, hereinafter referred to as 'clinical evaluation', where appropriate taking account of any relevant harmonized standards, must follow a defined and methodologically sound procedure based on:

1. Either a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, where:
   – there is demonstration of equivalence of the device to the device to which the data relates, and
   – the data adequately demonstrate compliance with the relevant essential requirements.
2. Or a critical evaluation of the results of all clinical investigations made.
3. Or a critical evaluation of the combined clinical data provided in 1 and 2."

Although being mandatory part in the process leading to CE marking for all device classes, CEV is a complicated procedure covering a wide scope of various fields of science and prone to limitations originating from device specific properties and regulatory attributes [5]. The CEV is a living process, consisting of a few steps, repeated when necessary, starting before obtaining the CE mark and continuing after placing the device on the market, in the latter case as part of the post-market surveillance system (for details on CEV see MEDDEV 2.7.1 CLINICAL EVALUATION: A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES (http://ec.europa.eu/growth/sectors/medical-devices/guidance_en).

Challenge in general

In the setting of the current legislation one could anticipate that similar problems with the tension between scientific objectivity and involvement in the important issues of our time, as seen in other areas of science, could arise [6]. Moreover, placing all the responsibility on the manufacturer, even when there is obligatory support by NB at conformity assessment procedures (in the case of class IIa, IIb and III devices), does not necessarily mean that a medical device has a real impact on relevant clinical outcomes. The issue of which clinical data are satisfactory for assuming medical evidence, e.g. the role of randomized clinical trials (RCT) in CEV, is nowhere defined. An odd situation can occur when a so-called equivalent device is already on the market and the manufacturer will affix the CE mark on a newly developed product asserting that this is an alternative. The grounds for equivalence can often be questioned. Another obstacle in the development of novel devices concerns differences in specific laws between countries or even regions. Approximation of laws relating to medical devices is largely advocated and hopefully will be addressed in the upcoming EU regulation [7].

Challenge at ideation/innovation phase

There is uncertainty and clear tension between promoting innovation and providing high-level clinical data as robust evidence of safety and performance. Decreasing the time spent on clinical investigation would have a beneficial economic effect for the producer, and hopefully for the health care sector, so long as the products are safe and effective. But how to achieve the sufficient prediction how much is enough, to establish the secure zone? Optogenetics is here a good example. It seems to have great diagnostic and therapeutic potential at least in cardiology, cardiac surgery, neurology, neurosurgery, and psychiatry. By applying pulses of light via an external or implanted light source to photo-sensitive tissue, electrical impulses can be induced in a closely selected region of tissue. Consequently it offers interesting modalities in diagnosis and treatment such as in cardiac pacing and neuro-stimulation [8, 9]. To speed up implementation of this and similar promising technologies one may refer to relevant technical standards such as those from the International Organization for Standardization, the International Electrotechnical Commission and similar. One should also promote actions directed at global collaboration involving academia, industry and authorities, development and adherence to standards, crossing frontiers ensuring homogeneity, and facilitating funding on the base of preliminary early health technology assessments. This could be of extreme importance in cases of very promising novel technology used for instance in plasmonic devices. These, by utilization of surface plasmon resonance (SPR), would revolutionize the diagnostic procedures [10]. The SPR allows for extremely high sensitivity and reproducibility, extraordinary rapid analysis, and could be a real-time information tool. Ongoing development of plastic based chips would allow for significant cost reduction.

Challenge at initial clinical evaluation phase

This may be illustrated by an example of a catastrophic complication of thrombosis which can happen during left ventricular assist device (LVAD) treatment. For properly selected patients presenting with advanced stage left ventricular heart failure, LVADs are life-sustaining, life-saving devices. Use of pulsatile flow LVADs were associated with some problems such as a rather high rate of mechanical failures, recipient size limitation due to relatively large sizes of the devices, and an annoying level of device sound. Development and introduction of the continuous flow LVAD, which has addressed the above-mentioned limitations, has been a large step forward. Initial studies showed fewer mechanical failures, superior infection rates, less noise generated, and an extended range of sizes. Even thrombosis rates were low in pivotal trials and post-marketing approval studies of HeartMate II (occurrence of thrombosis between 2% to 4%) [11]. Later, starting in 2011, unexpected pump thrombosis was observed. Alarming results on the thrombosis rates were reported in 2014 [12]. The confirmation of the findings was published 1 year later [13]. Could this be avoided? Solutions would be found in the guidelines for clinical evaluation as well as in rigorous adherence to the rules of genuine scientific scrutiny, creation of the honesty culture that flourishes better, more robust CI, preferably RCTs wherever possible, increasing the awareness about dangers in equivalence issues, and last but not least performing really longer long-term follow-up. The latter is a prerequisite in implantable devices and should be a landmark in trials in the premarket phase.

Challenge at post-marketing evaluation phase

The implantable cardioverter-defibrillator (ICD) can serve as an example of this challenge.

Some of the leading companies in the branch of ICD have experienced significant problems with their ICD leads. There were too many cases of externalized conductors, mechanical conductor cable wear, silicon insulation quality, and potential to fracture, forcing the companies to recall them [14]. The reasons for failures are various and include inadequate implantation technique, inherent weakness in device design, unexpected material wear at unusual exposures, intricate interferences between patient comorbidities and device features, to choose only a few factors. The complexity of such a milieu is overwhelming. Nevertheless, one can say that considering the late recalls, what happened is likely the result of difficulties in device post-marketing surveillance systems (PMS). Generally, even the best post-marketing safety monitoring incorporated in the company's quality system will not suffice if hospitals and other health care institutions lack reliable, rigorous reporting routines. That is the reason for the notorious serious adverse events underreporting for many devices. Physicians dealing with patients carrying ICDs or pacemakers play an important role in not only failure detection and optimal treatment of it but also in supplying the manufacturer with relevant data in a timely manner. Constant expansion of the clinical databases as well as device registries with their invaluable amount of reliable data would inspire the physician organizations and authorities to promote them into the realm of the device PMS. However, the medical community should, as soon as possible, agree on some basic keystones underlying the structure, aims and quality of registries to increase their transparency and ensure their robustness [15]. To serve as warning tool in the PMS context databases should be obligatory, exact, and extended to contain the variables required by the regulatory framework. Achieving this optimal goal would be easier if the present passive form of PMS were replaced by an active, real-time, self-analyzing, trend-detecting PMS system.

Challenge in ethics

Probably this is the greatest of all the challenges. All research has to impose the highest ethical standards to protect the participants. Fulfilling the principles of the Declaration of Helsinki is mandatory before any permission for a study can be obtained from the Ethics Committee in all EC member states. The CA do not allow any investigations

to start before approval is given by the Ethics Committee. Still scientific fraud is not excluded. The pressure on the part of scientists to accumulate many published papers implies that a niche has been created which meets the need for a quick publication process. Numerous, illegitimate, pseudoscientific journals have emerged. So-called "predatory publishing" practices have affected even the medical scientific field [16]. Every effort should be taken to support the work of such institutions as the international Committee on Publication Ethics (COPE) or initiatives like Jeffrey Beall's list of illegitimate journals. However, issues of transparency and trustworthiness will not be improved if not all actors on the scene, i.e. researchers, publishers, editors, reviewers, and medical associations, unite in the common great quest for Good Publishing Practices [17]. In a recently published paper a scandalous cheating technique was described. A big global publishing company confirmed that in 2015 one hundred and seven articles were retracted from its ten subscription journals and its open-access publisher BioMed Central. The reason was detection of fake email addresses and falsified peer review reports [18]. Is this only a disadvantage of the global internet? What about the personal moral values?

Nowadays, some questions need to be reassessed in order to find the best way for the quickest access of patients to innovative therapeutic devices without compromising their safety. These are major questions requiring immediate and deliberate attention: those associated with proper selection of the investigation, ethical problems generated by the regulatory framework and by extensive multicenter trials generating large aggregate data sets and results of meta-analysis, statistical consideration to avoid bias, and management of transparency in relations between manufacturers and researchers and doctors [19]. The appealing way to get maximum benefits for all involved would be diligent and generous sharing of information and clinical data. Although not free from several potential drawbacks, it seems to be an efficient way to obtain as much clinical evidence as possible and as fast as possible, which could overcome some of the weaknesses due to the short lifecycle of the medical devices [20].

Conclusions

Today, when progress is being made at cosmic speed, we must from time to time stop for a while to think... but don't think like Moniz, think like Hippocrates: *primum non nocere*.

In 1949, the neurologist António Egas Moniz received the Nobel Prize in physiology or medicine for his development of the prefrontal lobotomy – a procedure in which the connection is cut to a part of the brain (prefrontal cortex) in mentally ill, depressed or learning disabled people.

Disclosure

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