

The pre-market clinical evaluation of innovative high-risk medical devices

KCE reports 158C

The Belgian Health Care Knowledge Centre

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Executive summary

AIMS AND METHODS

Objective, Definitions and Scope

Medical devices range from basic equipment such as syringes and needles to heart pacemakers and drug-eluting coronary stents. Both in Europe and the US medical devices are categorised into different classes based on the risk they pose to patients, with class III devices representing the highest risk category.

The main reason for starting this project was the fact that Health Technology Assessment (HTA) agencies are repeatedly confronted with a relative lack of clinical data when assessing the value of innovative high-risk devices when they enter the market in Europe. This has led us to take a closer look at the pre-market clinical evaluation of such devices.

We discuss the pre-market clinical evaluation of innovative high-risk medical devices in Europe, and compare it with evaluations in the US. We also compare the evaluation of devices with the evaluation of medicines, where appropriate. In addition, issues on patient safety and transparency of information are studied. The timing of this report allows it to be taken into account by those involved in the ongoing rework of the EU Medical Device Directives. This effort should further improve the regulatory framework that supports the managed entry of new, safe and effective high-risk medical devices in the healthcare systems of EU Member States.

We define innovative high-risk devices in Europe as innovative class III devices and innovative implantable devices. In the US innovative high-risk devices (class III) typically undergo a pre-market approval (PMA) process.

In Europe, the pre-market clinical evaluation is defined as the assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer. Clinical safety is the absence of unacceptable clinical risks, when using the device according to the manufacturer's instructions for use. Clinical performance is the ability of a medical device to achieve its intended purpose as claimed by the manufacturer.

In the US, under the PMA process, each manufacturer must independently demonstrate "reasonable assurance of the safety and effectiveness" of the device for its intended use. The terms efficacy and effectiveness are not identical, but not always used consistently in the various regulations. Briefly, efficacy is assessed in a clinical trial setting while effectiveness refers to the efficacy seen under routine use conditions.

Study Methods

The following information sources were consulted in the conduct of this study.

- Experts of member organisations of EUnetHTA (a European network of HTA agencies) were consulted using an online forum.
- We checked the peer reviewed literature. However, the yield of this search was very poor, at least for descriptions and critical reviews of the European system when compared to the US.
- Some grey literature references were identified.
- European and US regulatory documents were checked.
- Representatives from Competent Authorities, FDA, Ethics Committees and the Medical Device Industry were consulted.

A draft of this report was presented and discussed at the EU Member State Chief Medical Officers Meeting, Liège, Belgium, November 2010, and at the EU Working Group on Clinical Investigation and Evaluation for Medical Devices (CIE WG), Brussels, May 2011.

CLINICAL DEVELOPMENT

The clinical development of medical interventions and technologies (medicines, devices, surgical techniques, etc.) for a given indication is characterised by different phases. This is reflected by the sequence of exploratory studies, often generating a hypothesis, followed by confirmatory studies to test the hypothesis. The sequence is illustrated in Figure 1. Active high quality post-marketing surveillance is also critically important. However, it cannot replace the pre-market evaluation.

Both the exploratory and the confirmatory phase take time and the sequence is essential. Confirmatory trials can only be designed properly based on the experience of using the device in exploratory trials in selected centres. Not only the device itself is studied but the complete system. This includes the most optimal procedures for handling the device and ways to shorten the learning curve. Specific attention should be given to ensure the external validity of the confirmatory trial. Also, the qualifications and training of the human operator beyond the trial setting are important as this human factor will co-determine the safety and effectiveness of the device in routine use.

These considerations should, however, not cast any doubt on the importance of RCTs as the highest standard to document clinical safety and to demonstrate any incremental efficacy, also for devices. RCTs with sham (or placebo) surgery as a comparator to prove device efficacy may sometimes be considered unethical. It may be more appropriate to document efficacy versus the reference treatment (watchful waiting, other device, drug treatment, surgery, etc.). In a recent report from the World Health Organisation, regulatory agencies have been called to ensure that, whenever possible, high quality randomised trials are completed prior to granting marketing approval. Experience at the FDA has shown that valid and realistic study designs are possible for the controlled evaluation of efficacy and safety of medical devices. The FDA considers RCTs to be critical for statistical validity and are ethical if designed according to current American Good Clinical Practices.

PRE-MARKET CLINICAL EVALUATION

Pre-Market Clinical Evaluation in Europe

The CE mark system (Conformité Européenne) used for medical devices is mainly based on the major Medical Devices Directive (93/42/EEC), which was amended in Directive 2007/47/EC. Novel high-risk medical devices do not undergo a pre-market review by Member States or European Authorities. The CE marking for innovative high-risk medical devices is applied by the manufacturer. The assessment of conformity with the essential requirements of the relevant Directives is checked by a Notified Body, a for profit organisation certified by a Member State Competent Authority. The latter vary between Member States; in some cases the national medicines agencies are endowed with the overview of medical devices; in other cases, specific agencies have been set up; and finally some Member States do not have any specific pathway for the approval of medical devices, relying purely on Notified Bodies.

This pre-market evaluation of a device by a Notified Body is performed only once for the complete European market. It includes the assessment and verification of the clinical evaluation by the Notified Body. In Europe, the clinical evaluation is defined as the assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer.

A company is free to choose any of the designated Notified Bodies. There are about 80 Notified Bodies currently designated for a total of 31 countries (in the European Economic Area – EEA). Companies may work with different Notified Bodies for different devices, and Competent Authorities are aware that companies could select a Notified Body that is likely to be less stringent in the assessment of a particular device.

Based on the grey literature and informal contacts with Competent Authorities, it seems that only a few pre-market studies of devices are randomised. Most are feasibility or performance trials, and “performance” completely depends on the extent of the clinical claim the manufacturer wants to make, if any. The studies rarely include a study hypothesis or sample size calculation and the number of patients evaluated varies by the indication, but is typically less than 100 patients (about 300 patients for drug eluting stents). It is important to note that the number of patients exposed and the pre-market trial design are not made public. Thus, we could not generate any hard statistics, despite the support of the Belgian Competent Authority. The guidance documents published do not provide any specific requirements on the depth and extent of pre-marketing clinical evaluations.

Based on a large subset of protocols that were reviewed in 2010, Ethics Committee representatives reported that, in Belgium, nearly all trials with high-risk devices were conducted after the CE mark had been obtained, and none of the identified pre-CE mark trials were randomised. Members of Ethics Committees and Competent Authorities are often confronted with a lack of clinical research expertise at small device companies. Likewise, insufficient clinical expertise has also been reported at the level of Notified Bodies. A study published in 2010 by the Dutch Competent Authorities found major shortcomings in the technical documentation of nine coronary stents, seven total hip implants and nine silver-containing wound dressings. In particular, concerning the clinical evaluation of the device, even Competent Authorities had to rely on a Google internet search to identify class III devices being marketed, as the comprehensive Eudamed database was not yet in full use. Mandatory use of the Eudamed database started on 1 May 2011.

Directive 2007/47/EC states that in the case of implantable devices and devices in Class III, clinical investigations shall be performed unless it is duly justified to rely on existing clinical data. After Directive 2007/47/EC became effective in March 2010, an increase in the number of clinical trials with high-risk devices was clearly seen, and some of these trials were randomised. For high-risk devices, a trial authorisation by the Competent Authorities is needed in each country where the trial is conducted, but the procedure differs significantly by Member State. Some Member States actively review the documentation submitted including the trial design. Other Member States have opted for the passive permission route (no review). The combination of a less stringent Notified Body and the possibility of passive permission thus still allows market entry of high-risk devices based on a minimal clinical data set, exposing very few (if any) patients to the device in the pre-market phase.

Pre-Market Clinical Evaluation in the US

In the US, pre-market device review procedures were introduced in 1976. The evaluations are performed by the FDA, mainly by its Center for Devices and Radiological Health (CDRH). Innovative high-risk medical devices should in principle follow a “pre-market approval” (PMA) procedure, typically requiring the conduct of a randomised controlled trial. Most other devices enter the US market using the 510(k), the “pre-market notification” route. This 510(k) process is faster, less stringent and less expensive.

Under the PMA process, each manufacturer must independently demonstrate “reasonable assurance of the safety and effectiveness” of its device for its intended use. Most PMA applications contain only a single study. In addition, many of the studies included in PMAs of cardiovascular devices have been shown to lack adequate strength, to lack coverage of specific study populations or to be prone to bias. In 2009, the FDA initiated an internal review and additionally commissioned the Institute of Medicine (IOM) to examine the medical device regulatory system and to issue recommendations. The IOM report is expected in mid-2011. Another recent initiative concerns the comparative effectiveness reviews in the US. The comparison of effectiveness data for drugs and devices will also be explored in this context.

Of importance is the fact that the US Centers for Medicare and Medicaid Services reimburse the cost of medical devices used in pre-market clinical trials if they meet certain criteria, up to the cost of a currently marketed, similar product.

HEALTH TECHNOLOGY ASSESSMENT

Payers increasingly look for evidence of efficacy to support coverage decisions. This is increasing the demand for clinical trials on devices and goes far beyond what is needed to obtain a CE label.

In Europe, safety and performance are to be demonstrated, whereas in the United States, the pre-market demonstration of safety and efficacy/effectiveness is required. This leads to entirely different clinical trials. For the demonstration of device performance, a randomised clinical trial is neither necessary nor appropriate whereas it is essential for the demonstration of clinical safety and efficacy in a controlled way. Device companies also tend not to make public the (limited) set of clinical data they collected in the pre-market phase in Europe.

There is a growing tension between early market introduction and product reimbursement as illustrated in Figure 1. Early market introduction in Europe can be situated in the exploratory clinical development phase, whereas payers increasingly want to see high-level evidence of efficacy (a completed confirmatory RCT for a specific indication) before reimbursing the device for that indication. This contrasts with the US where both market introduction and coverage by payers take place after completion of the confirmatory trial(s).

Table 1. The sequence of clinical development and timing of market introduction of novel invasive high-risk devices in Europe and the US.

	Theoretical sequence over time		
	Exploratory clinical trials	Confirmatory clinical trials (RCTs)	Health Technology Assessment
CE mark system in Europe	Market introduction based on single arm trials demonstrating safety and “performance”		Requires safety and efficacy/effectiveness data for the assessment
FDA PMA process in the US		Market introduction based on RCT demonstrating safety and “efficacy/effectiveness”	

Shortly after market introduction in Europe, companies may introduce a request for device reimbursement. At that time, a pre-market randomised trial evaluating efficacy and safety of the same device for the FDA is often initiated, sometimes conducted in part in Europe with CE marked products. At that stage, HTA agencies may already be asked to perform an evaluation of effectiveness and cost-effectiveness.

Recent examples of HTA evaluations include percutaneous aortic valves, endobronchial valves and interspinous devices. In each case, it was concluded that the available clinical evidence was not sufficient and that one should wait for RCT results before drawing conclusions. However, the results of an RCT conducted under a PMA often are not available until years after the device has obtained a CE mark. Postponing the reimbursement decision accordingly is often met with mixed feelings by industry and clinicians. More importantly, healthcare providers and patients in Europe are not informed about the added clinical value of such innovations before using them.

DISCUSSION

Few patients and even physicians are aware of the process by which medical devices are evaluated. Physicians in Europe, even including some chairs of Ethics Committees, generally but wrongfully assume that the pre-market clinical review of novel high-risk devices is highly comparable to the evaluation of medicinal products. For medicines, a rather complete sequence of clinical development is standard in the pre-marketing stage both in Europe and the US. For devices, regulations for pre-market clinical evaluation in Europe differ strongly from those in the US. Regulations in Europe (in contrast to the US) do not enforce the sequence of clinical development to be completed in the pre-marketing setting. The level of study evidence required in Europe is also much less specific compared with FDA requirements. Furthermore, the recent review of the medical device regulatory system in the US tends to widen the gap.

Another fact illustrating the difference in systems is that only one in five of the 8 500 medical device companies in Europe (probably fewer if one excludes companies belonging to a US group) have approached the US market. In addition, more devices of a particular type are often marketed in Europe compared with the US, e.g. 28 drug eluting stents are CE marked whereas only five have obtained FDA approval. Some devices continue to be marketed in Europe while having failed in the demonstration of efficacy in the RCT required in the context of a PMA in the US.

With regard to patient safety of medical devices, the major control point in Europe is post-marketing surveillance rather than pre-marketing as is the case for medicines. Post market surveillance is, however, hampered by an ongoing struggle both with under-reporting of the numerator (the number of adverse events) and lack of the denominator (the total number of exposures). Without active analysis, this important control point often remains an empty shell with a false reassurance of patient safety.

Randomised controlled trials should be considered as the highest standard to document efficacy and safety, also for innovative high-risk devices. How could one judge a 30-day mortality of 10% after the implantation of a percutaneous aortic valve based on a patient registry? Should this mortality be considered high or low compared with the standard of care? In the absence of an RCT, it is often impossible to judge.

Innovative high-risk medical devices account for only a minor proportion of all new devices. It should also be noted that for devices where only slight modifications were made to an existing device, an abbreviated development cycle may be perfectly appropriate, but this needs to be evaluated case by case.

A device cannot yet be considered to have an established routine clinical use when introduced on the market during the exploratory clinical development phase. Should this use be called experimental? For the patient, this can mean a more early access to a potentially lifesaving device, but at the risk of unknown efficacy and potential safety issues. Even excess mortality cannot be excluded as the clinical evaluation of the device is often very limited at that stage. Despite the increase in clinical trial activity induced by the EU Directive 2007/47/EC, the remaining variation in the stringency of clinical review both at the level of Notified Bodies and the Competent Authority level is not optimal to guarantee patient safety in a uniform way for EU citizens. Specific guidance by device type on trial design and endpoints to be measured in the pre-market phase would significantly help standardise the pre-market evaluations.

Instead of trying to streamline a very fragmented system of Notified Bodies and Competent Authorities, a more straightforward way to achieve the goals discussed before could be to centralise expertise at European level. This could, for example, be realised under the EMA umbrella, as was done for advanced therapy products.

Furthermore, there remains a lack of transparency of the pre-market clinical evaluation of innovative high-risk devices in Europe. We assume all pre-market clinical trial protocols state that the Declaration of Helsinki is respected, as is required in the Medical Devices Directive. This implies entering the trial in a publicly available trial registry before the first patient is entered. This also means publishing the results of the study, so physicians can fully inform their patients. In practice however, these clinical trials are most often not made public by the manufacturer.

In Europe, the responsibility to demonstrate clinical efficacy and further document patient safety (after marketing) is left to the marketing company, the professional societies and hospital directors. Hospitals may want to advertise the early adoption of innovative devices on their website, inducing other hospitals to follow suit. Awaiting inclusion of the device in the list of reimbursed devices, patients may be charged an important co-payment although the use of the new device may not be the best choice in terms of patient safety and efficacy. Introducing conditional reimbursement with evidence gathering in selected centres may stop this practice only in part.

The hypothesis that manufacturers generate a higher level of clinical evidence than that required by the regulators is unrealistic. Depending on the local policy of the company and the Member State, novel high-risk medical devices are first introduced in selected experienced centres or not. Unless the company strictly controls this market introduction, the expertise of the physicians using the high-risk device may vary considerably by Member State and potentially put the uninformed patient at risk.

In case of injury, it is often unclear to whom the liability claim needs to be addressed: is it the manufacturer? Is it the Notified Body who failed to make a proper assessment of the device? Is it the implanting physician, having neglected to make a proper risk assessment (what if the existing clinical data are not made public?) or having omitted to inform the patients on the risks?

What would be the consequences for industry if Europe moved away from requiring “performance” data only to also requiring pre-market data that demonstrate “clinical efficacy” for innovative high-risk devices?

Companies would see a delay in market introduction in Europe for such devices and potential lost sales. However, as payers become less willing to pay in absence of efficacy data, these sales might be lower than expected anyway.

Manufacturers who try to introduce the innovative high-risk device on the US market as well plan for the RCT investment. In order to lower the financial hurdle, payers in Europe should consider, as is the case in the US, co-financing of innovative high-risk devices used in pre-market clinical trials, provided that these trials are well-controlled and have clinically relevant endpoints.

Patients should be adequately informed of the possibility of participating in pre-market clinical trials of innovative high-risk devices. In such a setting, full patient information and written patient informed consent should be the rule. A more complete clinical evaluation in the pre-market phase will reduce the risk for the patient, not eliminate it. Post-market surveillance will remain necessary for detecting infrequent or long-term complications.

RECOMMENDATIONS^a

The long-term perspective at the European level

- For innovative high-risk devices, the future EU Device Directive should move away from requiring safety and “performance” data only to also require pre-market data that demonstrate “clinical efficacy or effectiveness”.
- Competent Authorities and Notified Bodies should ensure that, whenever possible, high quality randomised trials are completed with clinically relevant endpoints prior to granting marketing approval of innovative high-risk devices.
- Centralising the evaluation of high-risk devices at the European level might be a viable alternative and should be considered.
- The new pre-market procedure should result in an approved indication for the device and a publicly available product documentation including the full results of all trials. This transparency is required to allow physicians and patients to make an informed decision and HTA agencies to produce a correct assessment.
- European HTA agencies should jointly prepare an algorithm which clearly describes the clinical evidence necessary for a meaningful evaluation.
- Guidance documents for pre-market clinical trials by the type of high-risk device need to be developed. HTA agencies should also be involved in this activity.
- Payers in Europe should consider, as is the case in the US, co-financing of innovative high-risk devices used in pre-market clinical trials.
- The device industry should be made aware of the growing importance of generating clinical evidence and the specific expertise this requires.
- Patients should be informed that a more complete clinical evaluation in the pre-market phase will reduce the risk but not eliminate it.

Transient solutions at the member state level

- Awaiting a reworked Medical Device Directive, patient risk should be minimised at the Member State level by improving transparency with regard to the available clinical data and by limiting the market introduction of novel high-risk devices with minimal clinical data to centers with the necessary expertise. Preferably, this should be done under an appropriate research protocol (RCT if possible). This requires the commitment of the Competent Authorities, the marketing company, the physicians and the hospitals.
- The ethical issues associated with the early market introduction of innovative high-risk devices should be studied further by the commissions and organisations that provide ethical guidance to the physicians and hospitals.

^a The KCE is the only responsible for the recommendations given to the public authorities

Scientific Summary

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I WHY THIS REPORT?

At first glance, a report on the pre-market aspects of medical devices might be considered an unusual activity for agencies involved in Health Technology Assessment (HTA). Indeed, this development phase is controlled by the Competent Authorities of the Member States in Europe, and HTA typically takes place after market introduction. So why this report?

The goal of HTA agencies is to perform evaluations of clinical safety, effectiveness and cost-effectiveness of novel interventions and technologies such as innovative high-risk medical devices, thus informing the payers (for reimbursement decisions), healthcare providers and patients on the added value of such innovations.

The main reason for starting this project was the fact that HTA agencies are repeatedly confronted with a relative lack of clinical data when assessing the value of innovative high-risk devices when they enter the market in Europe. At the same time, a randomised controlled trial (RCT) is often initiated as a requirement for obtaining market access in the US. However, the results of such RCTs performed in conformity with US legislation often become available years after the device has obtained a CE mark. Postponing the reimbursement decision accordingly is often met with mixed feelings by industry and clinicians. This illustrates a growing tension between market introduction and the reimbursement of such products in Europe. This has led us to take a closer look at the pre-market clinical evaluation of such devices.

During this project, we discovered that EU Medical Device Directives are currently being reworked in order to further improve the regulatory framework that supports the managed entry of new, safe and effective high-risk medical devices in the healthcare systems of EU Member States. We hope that this report provides some timely input into this process.

In particular, we studied the following topics :

- The pre-market evaluation of innovative high-risk devices in Europe. This includes a comparison with the US system.
- Patient safety considerations in the case of early market introduction
- The lack of information and transparency
- Aspects of medicines regulations of relevance for devices

The findings are summarised in this brief report and form the basis for a number of policy recommendations.

Evidence of clinical efficacy is required before market entry in the US but not in Europe

Despite a recent increase of clinical data collected in the pre-market phase of the development of medical devices, the European system for approving medical devices is still based on a CE (Conformité Européenne) mark. This system is overseen by national Competent Authorities and a large number of Notified Bodies, for profit organisations certified by a Competent Authority. The latter vary between Member States; in some cases the national medicines agencies are endowed with the overview of medical devices; in other cases, specific agencies have been set up; and finally some Member States do not have any specific pathway for the approval of medical devices, relying purely on Notified Bodies. Overall, this system grants an early market introduction based on safety and device performance data only without any requirement to demonstrate clinical efficacy or effectiveness. This lack of clinical data often prevents HTA agencies from performing evaluations of clinical safety, effectiveness and cost-effectiveness when such innovative devices enter the market. Hence the payers, healthcare providers and patients are informed neither about the added clinical value nor about the risks of such innovations before using them.

In this regard, the European situation should be contrasted with the situation in the United States (US). In the US, innovative high-risk medical devices follow a Pre-market Approval (PMA) procedure, in which case the conduct of at least one randomised controlled trial (RCT) is typically required to prove clinical efficacy.

Patient safety may be put at risk in Europe

Second, patient safety may be put at risk, especially when high-risk (class III) medical devices, as defined later in this document, are granted early market access. The broad consequences of following the CE system for high-risk medical devices introduced to the European market should be examined more closely.

The lack of information and transparency

A third issue is the level of information about the clinical review of high-risk medical devices.¹ Few patients and even physicians are aware of the process by which medical devices are evaluated. Physicians in Europe, even including some chairs of Ethics Committees, generally but wrongfully assume that the pre-market clinical review of novel high-risk devices is comparable to the evaluation of medicinal products.

Transparency is also required in case the inventor of the device is the principal investigator in a clinical trial of the device, a situation that is not unusual.² More transparency is also needed when companies pay for their device to be demonstrated by opinion leaders.²

Aspects of medicines regulations of relevance for devices

The regulation of medicines commenced in the early 20th century in the US (e.g., the 1938 Food, Drug and Cosmetic Act) and intensified in the 1960s (e.g., the 1962 amendment requiring substantial evidence of effectiveness for all medicinal products). The formal regulation of medical devices started much later, i.e. in 1976 in the US and only in the early 1990s in the European Union (EU).³ Today, harmonisation of regulations between the regions of the world is more advanced for medicines than for devices.³ For medicines, for instance, the International Conference on Harmonisation (ICH) has harmonised parts of the assessment process between the European Medicines Agency (EMA), the US Food and Drug Administration (FDA) and the Japanese authorities; exchange of confidential data is now frequent before and after marketing authorisations. In this respect, ICH has also provided guidance on study design and endpoints of pre-market clinical trials by clinical indication.

2 DEFINITION, SCOPE AND METHODS

2.1 MEDICAL DEVICE DEFINITION

In Europe, the major Medical Devices Directive (93/42/EEC)⁴, as amended in 2007 (2007/47/EC)⁵, defines a medical device as any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software 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.

Medical devices include basic equipment such as syringes and needles but also heart pacemakers, hip prostheses, coronary stents and ultrasound or X-ray equipment for diagnostic or therapeutic use.³ Both in Europe and in the US, devices are categorised into different classes based on the risk they pose to patients, with class III devices representing the highest risk category.

2.2 STUDY SCOPE

We discuss the pre-market clinical evaluation of innovative high-risk medical devices in Europe and compare it with the US. We define innovative high-risk devices in Europe as innovative class III devices and innovative implantable devices. In the US, innovative high-risk devices (class III) typically undergo a pre-market approval (PMA) process.

Innovative high-risk medical devices account for only a minor proportion of all new devices. As the risk related to their clinical use is considered high, an appropriate and proportionate pre-market clinical evaluation is expected. It should also be noted that for devices where only slight modifications were made to an existing device, an abbreviated development cycle may be perfectly appropriate, but this needs to be evaluated case by case. The pre-market evaluation is broader than clinical testing. However, in this report we do not cover the pre-clinical evaluation nor the manufacturing practices for the devices. For example, before devices are implanted in patients, it may be necessary that such devices are first tested in appropriate animal models. In this report, we focus on the clinical review only.

Our conclusions should not be extrapolated to the vast number of lower risk devices outside the study scope. Advanced therapy medicinal products (including gene therapy and tissue engineering) may in part overlap with medical devices and have specific challenges,⁶ but these are not covered here.

We also do not question the importance of active, high quality post-marketing surveillance in addition to the pre-market evaluation. Post-market surveillance, however, cannot replace a pre-market evaluation. Post-marketing activities are not within the scope of this study.

In Europe, the pre-market clinical evaluation is defined as the assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer. Clinical safety is the absence of unacceptable clinical risks, when using the device according to the manufacturer's instructions for use. Clinical performance is the ability of a medical device to achieve its intended purpose as claimed by the manufacturer.

In the US, under the PMA process, each manufacturer must independently demonstrate “reasonable assurance of the safety and effectiveness” of the device for its intended use. The terms efficacy and effectiveness are not identical, but not always used consistently in the various regulations. Briefly, efficacy is assessed in a clinical trial setting while effectiveness refers to the efficacy seen under routine use conditions.

2.3 STUDY METHODS

This project was initiated based on the experience of the Belgian HTA centre, known as the Belgian Health Care Knowledge Centre (KCE), after having conducted several HTAs for high-risk innovative devices.⁷⁻⁹

We consulted the peer reviewed literature using a Medline search. The yield of this search was very poor, at least for descriptions and critical reviews of the European system when compared to the US. During the finalisation of this report, a series of articles on European medical device regulations were published in the British Medical Journal^{1, 2, 10-12}. Also, a policy report by the European Society of Cardiology was then published.¹³

The poor yield is illustrated by a search (rerun June 11, 2011) based on (“Medical Device” or “Medical Devices”). We found only 30 hits when combined with (“Notified Body” or “Notified Bodies”), 29 hits when combined with (“Competent Authority” or “Competent Authorities”), 546 hits when combined with (“EU” or “Europe” or “European”) and 1193 hits when combined with (“FDA” or “Food and Drug Administration”).

We tried a search of the web using Google, and found some grey literature references. The European Directives and regulations and FDA documents were consulted using the web. In addition, the following information sources were consulted in the conduct of this study.

- Experts of member organisations of the European network of HTA agencies (EUnetHTA) were consulted using an online forum; some became co-authors of this report.
- Representatives from the Competent Authorities of Belgium, UK, Ireland, The Netherlands and France were contacted.
- Meetings were held at KCE with representatives of Ethics Committees and the Medical Device Industry.
- Comments on a draft document were obtained from the FDA Center for Devices and Radiological Health, Division for International Assistance.

A draft of this report was presented and discussed at the EU Member State Chief Medical Officers Meeting, Liège, Belgium, November 2010, and at the EU Working Group on Clinical Investigation and Evaluation for Medical Devices (CIE WG), Brussels, May 2011.

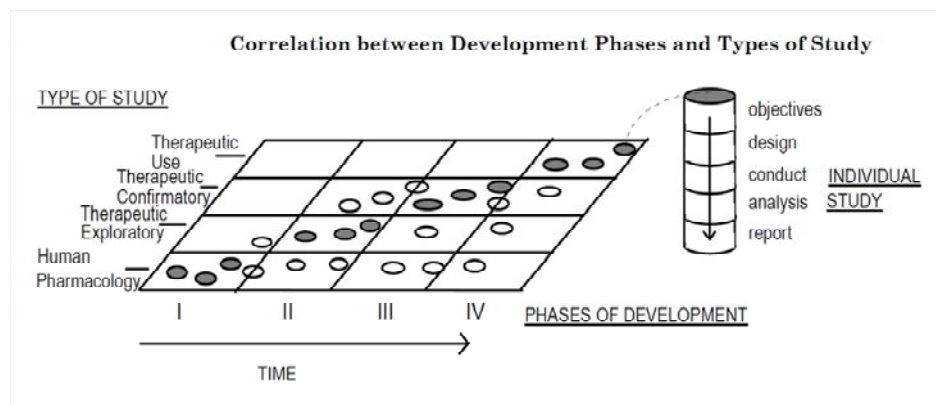
3 CLINICAL DEVELOPMENT OF DRUGS AND DEVICES

3.1 CLINICAL DEVELOPMENT PHASES

Exploration followed by confirmation

The clinical development of medicinal products is characterised by different phases (Figure 1).¹⁴ In terms of study types, this is reflected by the sequence of exploratory studies, often generating a hypothesis, followed by confirmatory studies testing the hypothesis.

Figure 1. Clinical development phases and types of studies for a medicinal product



This matrix graph illustrates the relationship between the phases of development and types of study by objective that may be conducted during each clinical development of a new medicinal product. The shaded circles show the types of study most usually conducted in a certain phase of development, the open circles show certain types of study that may be conducted in that phase of development but are less usual. Each circle represents an individual study. To illustrate the development of a single study, one circle is joined by a dotted line to an inset column that depicts the elements and sequence of an individual study. Source: ICH Guideline, General Considerations for Clinical Trials, 1997¹⁴

Ideally, the clinical development of novel high-risk medical devices for a specific indication should be characterised by an exploratory phase followed by a confirmatory phase, typically an RCT, even though both phases take time. One important aspect of clinical development is that RCTs can only be designed properly based on the experience of using the device in exploratory trials in selected centres, where not only the device itself but the complete system, including the most optimal procedures for handling and use of the device and shortening the learning curve, is studied. In contrast to most medicines, high-risk devices are typically not tested in healthy volunteers.

Introducing safe and effective devices often requires more than conducting trials

Specific attention should be given to ensure the external validity of the trial and in particular the necessary qualifications and training of the human operator beyond the trial setting. This human factor will often co-determine the later safety and effectiveness of the device in routine use. This consideration should not cast any doubt on the importance of RCTs as the highest standard to document clinical safety under controlled conditions and to demonstrate any incremental efficacy, also for devices. For example, in the absence of well-controlled trials, it may be impossible to judge if a 30-day mortality of 10% after the implantation of a percutaneous aortic valve should be considered high or low.⁷

Comparative trials are essential

The choice of the comparator should in most cases be the standard of care for the target patient population. The standard of care can be watchful waiting, optimal pharmacological treatment, surgical intervention or the use of another device.

Sometimes, the standard RCT study design will need to be adapted to take into account the specificities of devices and the expertise of the centre, e.g. randomised patient referral to a nearby study centre specialising in one of the studied interventions. High quality RCTs can also be conducted with devices.¹¹ Experience at the FDA has shown that valid and realistic study designs are possible for the controlled evaluation of efficacy and safety of medical devices.

The gap with the US may widen

In contrast to medicines where a rather complete sequence of clinical development is standard in the pre-marketing stage, the regulation of devices in Europe (in contrast to the US) do not enforce the completion of this sequence in the pre-market setting. Despite the creation of a Global Harmonisation Task Force (GHTF) for device regulations in 1992 (www.ghrf.org),³ the pre-market regulations of the FDA and Europe remain very different. In addition to an internal review by the FDA, the Institute of Medicine (IOM) is in the process of assessing whether the FDA's clearance process protects patients as well as it can without limiting improvements in medical devices. (<http://iom.edu/Activities/PublicHealth/510KProcess.aspx>) This review of the medical device regulatory system in the US might widen the gap. The European system is based on the demonstration of safety and performance, whereas the US system requires the pre-market demonstration of safety and efficacy/effectiveness. This leads to entirely different clinical trials. For the demonstration of device performance, an RCT is neither necessary nor appropriate, whereas it is essential for the demonstration of clinical safety and efficacy in a controlled way. The level of study evidence required in Europe is also much less specified compared with the FDA requirements for a PMA application.

3.2 HEALTH TECHNOLOGY ASSESSMENT

A growing tension between early market introduction and product reimbursement

HTA agencies perform evaluations of clinical safety, effectiveness and cost-effectiveness of novel interventions and technologies. Evidence of effectiveness is increasingly requested by the payers to support coverage decisions,¹⁵ increasing the demand for clinical trials on devices. This goes far beyond what is needed to obtain a CE label. In addition, HTA agencies also have a role in informing healthcare providers and the patients about the added value of a new medical technology or intervention.

Table 1. The sequence of clinical development and timing of market introduction of novel high-risk devices in Europe and the US.

	Theoretical sequence over time		
	Exploratory clinical trials	Confirmatory clinical trials (RCTs)	Health Technology Assessment
CE mark system in Europe	Market introduction based on single arm trials demonstrating safety and "performance"		Requires safety and efficacy/effectiveness data for the assessment
FDA PMA process in the US		Market introduction based on RCT demonstrating safety and "efficacy/effectiveness"	

This growing tension between early market introduction and product reimbursement is illustrated in Table 1. Early market introduction in Europe can be situated in the exploratory clinical development phase, whereas payers increasingly want to see high-level evidence of efficacy (a completed confirmatory RCT for a specific indication) before reimbursing the device for that indication. This contrasts with the US where both market introduction and coverage by payers take place after the completion of confirmatory trial(s).

Companies may introduce a request for device reimbursement in European countries while the pre-market randomised trial evaluating efficacy and safety of the same device for the FDA is being started, sometimes conducted in part in Europe with CE marked products.^{16, 17} At that stage, HTA agencies such as the Belgian KCE may be asked to review the evidence, and will most often have to conclude that one should wait for the RCT results before drawing valid conclusions. This was the case in three rapid assessment HTA reports by the KCE covering percutaneous aortic valves, endobronchial valves and interspinous devices.⁷⁻⁹

The timing of market entry in Europe and the US and the supporting pre-market clinical studies that are in the public domain are listed in Table 2 for the devices evaluated in these three KCE reports. Note that it is not possible to find out how many patients were exposed nor the trial design used to obtain the CE mark. A system of regulatory approval for devices that lacks even a basic level of transparency for independent evaluation (such as HTA) seems unacceptable.¹

Table 2. Pre-market clinical data for innovative high risk devices covered in KCE reports, a comparison of market introduction and the supporting studies (including design and patient numbers).

Device	Clinical data for CE mark	Clinical data for FDA approval
Medtronic CoreValve Percutaneous Aortic Valve (PAV)	March 2007, patients exposed ?	RCT: 1377 patients, start 2010.
Edwards Sapien PAV transfemoral	September 2007, patients exposed ?	RCT PARTNER-US: 1040 patients, start 2007.
Edwards Sapien PAV transapical	December 2007, patients exposed ?	RCT PARTNER-US: 1040 patients, start 2007.
Spiration IBV system (intra bronchial valve)	Before March 2007	RCT: 300 patients, 2007 - 2009.
Pulmonx/Emphasys Endobronchial Valve (EBV)	2003?	RCT VENT: 270 patients planned, started 2004, 321 enrolled, results published 2010. PMA submitted October 2007. No FDA approval ?
Medtronic X STOP Interspinous Process Distraction System	July 2002, patients exposed?	RCT: 191 patients, 2000-2003. FDA approval: November 2005.
Paradigm Spine COFLEX - Interspinous implant	December 2006, patients exposed?	RCT : 460 planned, start 2006, enrollment complete 2010: 380 patients.
Paradigm Spine COFLEX-F - minimally invasive lumbar fusion	December 2006, patients exposed?	?
Medtronic (Sofamor Danek) DIAM Spinal Stabilization System	Before 2006, patients exposed? Note: post-marketing RCT (268 patients, 2006 – 2013)	RCT: 306 patients, 2006 - 2013. RCT: 26 patients, 2008 -2010.

? = information not publicly available

Other consequences of the different systems in Europe and the US

It should be noted that additional CE marked devices exist that are not listed below because no clinical trial activity for an FDA submission or FDA approval could be detected. This illustrates a poorly documented effect of the difference in regulatory systems: only one in five of the 8 500 medical device companies in Europe (probably fewer if one excludes companies belonging to a US group) has approached the US market.¹⁸ In addition, more devices of a particular type are often marketed in Europe compared with the US, e.g. 28 drug eluting stents are CE marked whereas only five have obtained FDA approval. Unfortunately, it is not uncommon that negative trials are not made public. Also, final negative decisions on PMA dossiers are not made public on the FDA website. Therefore, it cannot be excluded that devices continue to be marketed in Europe while having failed in the demonstration of efficacy in the RCT required in the context of a PMA in the US, as illustrated by a negative FDA panel vote for an endobronchial valve system in 2008.¹⁹ Several similar examples are given in a recent paper by Cohen and Billingsley.¹⁰

4 PRE-MARKET DEVICE REVIEW IN THE US

Two pre-market device review procedures

In the US, the FDA (mainly its Center for Devices and Radiological Health, CDRH) performs the pre-market evaluation of all devices. For device-drug combinations, another FDA centre may take the lead. In 1976, two pre-market device review procedures were introduced in the US: the “pre-market approval” (PMA) and the “pre-market notification,” often referred to as “510(k)”. Different classes of devices exist based on the risk they pose to patients. Class I devices are low risk and most are exempted from any pre-market review (subject to limitations). Class II devices present moderate risks to patients and class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health or present a potential, unreasonable risk of illness or injury. In the period from 2002-2007, of the roughly 50 000 devices that entered the market, 71%, 26% and 2% were class I, II and III respectively.²⁰

Compared with the PMA process, the 510(k) route is faster, less stringent and less expensive.²⁰ For devices which are claimed to be “substantially equivalent” to a device already cleared as a 510(k), known as the predicate device, a 510(k) submission is used, which includes performance characteristics that support equivalence. Overall, 85% to 90% of the 510(k)s contain no clinical data.²⁰ High-risk devices that were on the market before 1976 could be sold under the 510(k) provision. However, new devices that the manufacturer deems to be “substantially equivalent” to such a high-risk device could also win approval under the 510(k) process.²¹ The assumption of equivalence may be stretched, as for example the 510(k) clearance of virtual colonoscopy image analysis software, for which no clinical benefit was demonstrated before marketing.²² For certain class II devices cleared for marketing using a 510(k) procedure, e.g. dynamic stabilisation systems and components for spinal fusion,⁹ the FDA is considering the need for additional preclinical and clinical testing requirements based on post-market surveillance information.¹⁹

The pre-market approval process

For innovative and high-risk devices without a predicate device, representing 79% of the class III devices, a PMA application is needed, the most stringent type of device marketing application required by the FDA.²⁰ Under the PMA process, each manufacturer must independently demonstrate “reasonable assurance of the safety and effectiveness” of its device for its intended use. Note that the FDA wording for medicines is stronger, requiring “substantial evidence of effectiveness”. In order to start research trials in the US to be included in a PMA, the sponsor first needs to obtain an Investigation Device Exemption (IDE) approval from the FDA.²³ The US Centers for Medicare and Medicaid Services (CMS) will reimburse the cost of medical devices studied under IDE if they meet certain criteria. The level of reimbursement is up to the cost of a currently marketed, similar product. For diseases or conditions affecting small patient populations (under 4000 patients in the US), the FDA, since 1996, has allowed humanitarian device exemption (HDE) applications, which are similar in both form and content to a PMA application but are exempt from the effectiveness requirements of a PMA. In addition, an HDE differs from a PMA in many other ways such as fees and review timelines.

For a PMA, the FDA requires the study evidence on which device approval is based to be of high quality and ideally consisting of randomised, double-blind studies (pivotal trials). However, most PMA applications contain only a single study.²⁰ In addition, many studies included in the PMAs for cardiovascular devices have been shown to lack adequate strength, to lack coverage of specific study populations or to be prone to bias.^{20, 24, 25} The FDA may call on an advisory panel, but is not bound by those recommendations.²⁶ Recent high-profile cases involving potentially dangerous defects in widely used cardiovascular devices have increased concerns about the adequacy of pre-market trials and post-market surveillance in establishing the safety of these devices^{27, 28}. Problems with effectiveness are not as readily apparent once a device is on the market, in part because post-market efficacy/effectiveness trials of approved devices are rare.²⁰

The consequence of this historical and legislative artifact in the US is that clinical data that would never be sufficient to support the approval of a drug can result in approval of a device and divert patients from an effective drug to a less effective device.²² In 2009, the FDA started an internal review and additionally commissioned the Institute of Medicine (IOM) to examine the medical device regulatory system and to issue recommendations. The IOM report is expected mid-2011. Another recent initiative concerns comparative effectiveness reviews in the US.²⁶ The comparative effectiveness of drugs and devices used for the same indication will also be explored in this context.

5 PRE-MARKET EVALUATION IN EUROPE

5.1 THE SYSTEM OF CE MARKING

In contrast to the US, in Europe novel high-risk medical devices do not undergo a pre-market review by Member States or European Authorities. Instead, they have to go through a system of CE marking, the purpose of which is to indicate that the device performs as labelled and that no safety issues were identified. The CE marking for high-risk novel medical devices is applied for by the manufacturer and the conformity assessment is checked by a Notified Body. Notified Bodies are for-profit organisations certified by a Member State Competent Authority. It is important to note that the aim of pre-market clinical studies is to illustrate safety and performance, not to prove efficacy.

For most low risk devices (class I, e.g. wheelchairs, adhesive bandages, etc.), the manufacturer is allowed to affix a CE mark (self-certification) and to register the product with a national Competent Authority.³ The national Competent Authorities will check through their audit and inspection programmes to ensure that the manufacturer has complied with all the requirements. It should be noted that the CE marking system is also applied to many non-medical products.

Notified Bodies

Notified Bodies perform conformity assessments or pre-market reviews (including clinical data review) of active implantable medical devices, class II and III devices, and class I devices with a measuring function or supplied under sterile conditions.³ All Competent Authorities have a system of auditing Notified Bodies; in addition, a system is in place to ensure uniformity of auditing. For instance, the Competent Authority will audit the relevant Notified Body located in its country if safety issues with a marketed device are reported. For drug-device combination products where a scientific opinion from a national medicinal competent authority or from the EMA has been sought, the Notified Body is expected to consider the comments of these medicines agencies but remains free to make the final decision on the device. In the case of devices containing a human blood derivative, the Notified Body can only decide positively if the EMA's scientific opinion is favourable.³

A company is free to choose any of the designated Notified Bodies. There are about 80 Notified Bodies currently designated for a total of 31 countries in the European Economic Area (EEA). Companies not present in the EEA have to appoint an authorised representative within the EEA.²⁶ Notified Bodies are not on a level playing field in terms of their criteria for approval.²⁹ Some Notified Bodies have only two or three staff.¹⁰ Companies may work with different Notified Bodies for different devices and Competent Authorities are aware that companies could select a Notified Body that is likely to be less stringent in the assessment of a particular device.¹⁰ The Notified Body Operating Group (<http://www.nbog.eu/>) is working on this issue and a rewrite of the device directives is expected to provide a solution.³⁰ The pre-market evaluation/certification of a device by a Notified Body, resulting in a CE label, is performed only once for the entire European market. There is, however, a safeguard clause which Member States can invoke if evidence of a major public health concern is identified. Recertification of the device is performed by the Notified Body typically after 3 to 5 years.

5.2 PRE-MARKET CLINICAL TRIALS

Pre-market clinical trials in Europe are not made public

In the absence of robust and public statistics, we have tried to conduct a survey among the Notified Bodies on the number of patients exposed and the type of trial design used before a CE mark is applied to a novel high-risk device. Three major Notified Bodies were requested by the Belgian Competent Authorities to complete a simple questionnaire on the number of patients exposed to the innovative device pre-CE mark and on the type of trial design (randomised or not). This information (without identification of the device) was requested for cardiovascular implantable devices with or without an active substance and for other implantable devices with an active substance. Unfortunately, no reply was obtained within the timeframe of the project. Collecting this type of data turns out to be very difficult, if not impossible.

This was also the case for 192 recalled devices when researchers from the UK tried to obtain pre-market clinical data from the manufacturers and six Notified Bodies.^{1,31} Only four companies (2%) provided any clinical data. Confidentiality seems to overrule transparency in Europe much more than in the US.¹⁰

Similarly, Competent Authorities in the Netherlands (legally entitled to control the industry) encountered difficulties in obtaining technical documentation of class III devices from industry.³² Devices studied included nine coronary stents, seven total hip implants and nine silver-containing wound dressings. It is of interest to note that even Competent Authorities have to rely on a Google internet search to identify class III devices being marketed in Europe (as there is no comprehensive list or database yet). The report states that major shortcomings were identified in the documentation received, in particular concerning the clinical evaluation of the device.³²

The report does not provide specific information on trial design or subjects exposed. Based on the grey literature²⁹ and informal contacts with the Competent Authorities, it seems that studies rarely include a study hypothesis or sample size calculation²⁹ and that the number of patients evaluated varies by the indication but is typically less than 100 patients. These studies are often referred to as single arm “feasibility” trials or “performance” trials. Only for drug-eluting stents is the minimum number of patients exposed in the pre-market phase more or less in the public domain. Based on the potential safety issues that were identified, the number of patients studied increased over time from 50 to 300 (no RCT required). It is very important to note that an evaluation of clinical efficacy is not part of the pre-marketing evaluation in Europe.

Based on a large subset of protocols that were reviewed in 2010, representatives of Belgian Ethics Committees reported that nearly all trials with high-risk devices in Belgium are conducted after the CE mark has been obtained, and that the identified pre-CE mark trials were not randomised.

Members of Ethics Committees and Competent Authorities are often confronted with a lack of clinical research expertise at small device companies. Unfortunately, Notified Bodies may also lack the expertise to interpret clinical data and clinical safety signals.¹ In this regard, the European Society of Cardiology has recommended that independent expert physicians should be involved in reviewing decisions of new class III devices.¹³

Some positive news

The positive news, however, is that, based on information informally obtained from the Competent Authorities of several Member States, the number of clinical trials with high-risk devices has clearly increased after March 2010 when Directive 2007/47/EC, became effective. Some of these trials are randomised. Before the start of a trial, the manufacturer must notify the Competent Authority of a proposed Clinical Investigation and must submit the required information. In the UK, 64 clinical investigations on medical devices were notified in 2009. It is recommended but not mandatory to discuss the design with the Notified Body or a Competent Authority.²⁶

For high-risk devices, trial authorisation by the Competent Authorities is needed in each country where the trial is conducted, but the procedure differs significantly by

Member State. Some Member States actively review the documentation submitted, including the trial design. Other Member States have opted for the passive permission route (no review). The combination of a less stringent Notified Body and possible passive permission continues to allow market entry of high-risk devices based on a minimal clinical data set, without exposing any patient, or only a very low number of patients, to the device in the pre-market phase.

5.3 REGULATIONS

The Directives

In the European Economic Area, the Active Implantable Medical Devices Directive (90/385/EEC), covering cardiac pacemakers and other active implantables was introduced in July 1993. The major Medical Devices Directive (93/42/EEC) covered all other devices (excluding in vitro diagnostics), and had a transitional period until July 1998. The In Vitro Diagnostics (IVD) Directive 98/79/EC was introduced in June 2000 with a three year transitional period.⁴ In 2007, the previous directives were amended by Directive 2007/47/EC, which became effective in March 2010.⁵ The Medical Devices Directives define four categories of device, graded accordingly to the risk assessment (I, IIa, IIb, III). The essential requirements are the standards which have to be met by the manufacturer. The directives require manufacturers to report all serious adverse incidents to the National Authorities under the so-called Mandatory Vigilance scheme. Only the Directives are legally binding documents; they are underpinned by standards and by guidance documents.³ The standards are elaborated by the European Standards Group and many were subsequently adopted into international standards by the ISO (International Standards Organisation). There are also technical guidance documents (so-called MEDDEV documents), which are generated by the European Medical Device Expert Group convened by the European Commission.³ In 2009, the Directorate General for Health and Consumer Affairs (DG Sanco) became responsible for medical devices within the European Commission (before 2009, DG Enterprise was responsible).

The use of the European database on medical devices (EUDAMED) is obligatory as of May 2011.³³ It will contain information on manufacturers and authorised representatives, on devices and certificates, and on vigilance and clinical investigations (protocol title and primary objective only, entered by the Competent Authority where the trial is notified first). In the future, this database will thus serve as a non-public registry of device clinical trials. It will, however, not contain trial design information. A medical device working group is drafting non-public summary device information report that should also be available through EUDAMED in the future, and which may get updated with post-marketing data. The need for a public trial registry has also been discussed.³⁴ The Medical Devices Directive mentions that clinical trials should adhere to the Declaration of Helsinki.³⁵ This implies entering the trial in a publicly accessible trial registry before the first patient is recruited. It remains unclear whether this requirement is actively checked by all Competent Authorities and Ethics Committees granting the conduct of a trial. The Declaration of Helsinki also requires that the results of the study are published, so physicians can fully inform their patients. In practice, however, the pre-market clinical trials in Europe are most often not made public by the manufacturer.

Clinical investigations shall be performed unless it is duly justified to rely on existing clinical data

Many manufacturers continue to successfully support their class I and II devices in Europe with published data only, demonstrating conformity or similarity to a marketed device. The conduct of prospective trials for higher risk devices is still not mandatory. If conducted, most are non-randomised, single arm studies. Directive 2007/47/EC states that, in the case of implantable devices and devices in Class III, clinical investigations shall be performed unless relying on existing clinical data is duly justified.⁵

The EC (European Commission) published the MEDDEV 2.7.1 Appendix I in December 2008, the MEDDEV 2.7.1 Rev.3³⁶ in December 2009, and the MEDDEV 2.7/4 guidelines³⁷ in December 2010. These documents are designed to help manufacturers and Notified Bodies in the clinical evaluation of medical devices. MEDDEV 2.7.1 Appendix I covers the clinical evaluation of coronary stents. The wording on trial design enforcing randomised trial(s) is not strong and a single arm study design can still be selected by the device company: *“Controlled clinical trials shall be conducted when necessary to substantiate claims made by the manufacturer. The demonstration of the benefit-risk profile of the stent system under investigation may require a randomised comparative study design.”* In general, it remains unclear how a benefit-risk analysis can be conducted in case only device performance (and not clinical benefit) has been assessed.

The 2009 revision 3 of MEDDEV 2.7.1 was based on the Global Harmonisation Task Force (GHTF)'s international regulatory guidance document on clinical evaluation (SG5/N2R8:2007). The December 2010, MEDDEV 2.7/4 guidelines³⁷ were based on the SG5/N3:2010 guidance document of the GHTF. However, for high-risk devices, this guidance does not provide any specific requirement on the depth and extent of the pre-marketing clinical evaluations. The clinical evaluation and its outcome shall be documented and included and/or fully referenced in the technical documentation of the device.⁵ The guidance mentions that all data sets should be included. However, there is no publicly available summary describing the basis for granting a CE mark¹⁰ and there is no obligation to include the results of all clinical studies in the product insert. A reason mentioned by industry representatives (but not supported by data) for not making the results of clinical trials public is the relatively weak intellectual property protection of medical devices when compared to medicinal products. In addition, Directive 2007/47/EC specifies that all parties involved in the application of the Medical Devices Directives are bound to observe confidentiality with regard to all information obtained in carrying out their tasks.⁵ Should these arguments outweigh considerations on patient safety and the provisions of the Declaration of Helsinki, which are also required to be followed according the same Directive⁵?

6 ETHICAL AND MEDICO-LEGAL ASPECTS

6.1 PATIENT INFORMED CONSENT

The use could be called experimental

The regulations in Europe allow an early market introduction for high-risk medical devices at a time when the device cannot yet be considered to have an established routine clinical use indication, suggesting the use could be called experimental. Often, the confirmatory clinical development phase is still to be initiated or is ongoing. For the patient, this can imply earlier access to a potentially lifesaving device, but at the risk of insufficiently demonstrated efficacy and potential safety issues. In addition, there is an often-raised argument that conducting trials hampers innovation, and that RCTs with devices are more complex to conduct compared to drugs. One concern is that RCTs for devices performing sham (or placebo) surgery as comparator is not considered ethical. Whereas such design can prove efficacy, it may be more appropriate to document efficacy versus the reference treatment (watchful waiting, device, drug, surgery, etc.). The idea of patient safety versus innovation seems to be central to the debate as to whether Europe should go for pre-market regulations similar to those of the US. Awaiting the possible implementation of changes to the Medical Devices Directive, it is crucial to consider transitional measures, guaranteeing optimal transparency regarding the safety risks to patients treated with high-risk medical devices in the post-market but still experimental phase in Europe.

Specific guarantees or patients' rights are lacking

Patients treated with a high-risk medical device in the experimental phase are often not aware of the risks and specific guarantees, or patients' rights are lacking or are often unclear. European regulations of medical trials and research ethics (e.g. the Declaration of Helsinki, The European Convention on Human Rights and Biomedicine, The Clinical Trials Directive) are mainly focused on clinical trials and consider the scientific responsibility for protection of the dignity, integrity, vulnerability and rights of the human person as a basic ideal. Hence, several guarantees, such as systems of research Ethics Committees, written informed consent, specific liability systems, etc. have been integrated in legislation. Yet, there seems to be no reason to grant less protection to patients who are treated with a high-risk medical device in the experimental phase outside the context of a trial than to those patients who participate in a trial.

Although innovative techniques and devices raise numerous general ethical questions for society (e.g. equity, choices in healthcare, etc.), in the next paragraphs, we will focus on the most important legal-ethical topics from the patient's point of view.

The European Convention on Human Rights and Biomedicine

The European Convention on Human Rights and Biomedicine (<http://www.conventions.coe.int/Treaty/en/Treaties/Html/I164.htm>) intends to protect the rights of patients for preventive, diagnostic, therapeutic and research applications.³⁸ The majority of the EU Member States have signed it (but not Belgium, UK, Germany, Austria, etc.) and a number have ratified it. Countries that have not signed this convention may have developed their own legislation to protect patients' rights. Most widely accepted general patients' rights are incorporated in the Convention, such as the right to be adequately informed, the right to freely give or refuse consent to a medical intervention, the right to equitable access to healthcare etc. Yet, these rights are formulated in a very general way, and the application to the particular situation of high-risk medical devices in an experimental phase, outside the context of a clinical trial, is unclear.

In the experimental phase after early market introduction, outside the context of a trial, there are no laws specifically targeting the topic of patients' rights. It is interesting to take a closer look at the extent to which "general" patients' rights are able to guarantee the necessary protection for patients in this situation. The right to informed consent, which is particularly relevant for this topic, is guaranteed in all Member States that enacted a patients' rights act. There are however, numerous differences in the modalities. It is therefore necessary to study the details in legal rules in every Member State. As this falls out of the scope of this project, we limit ourselves to give the example of the Belgian Patients' Rights Act.³⁹

The Belgian Patients' Rights Act

In principle, informed (oral or written on the patient's or the physician's demand) consent is needed for every medical intervention of a health care professional (art. 8 § 1 Patients' Rights Act). Consequently, the patient needs to consent to the treatment with a high-risk medical device. The problematic issue with regard to high-risk medical devices relates to the content of the information. The Patients' Rights act states that this information should include the aim, the character, the urgency, the period, the frequency, the relevant contra-indications, the side-effects and the risks of the intervention, the aftercare, the possible alternatives and the financial consequences (art. 8 § 2). This is a non-exhaustive list. It is up to the treating physician to complete the information to the extent he/she assumes necessary for the patient to give informed consent. What should be understood by the "risks" of the intervention? Does this concept mean that the healthcare professional is obliged to inform the patient of the risk linked to the use of the high-risk medical device in the stage of early market introduction? It seems rather impossible for the physician to inform the patient in this regard, since there is no public document summarising the available clinical data at the moment of market introduction of novel high-risk devices in Europe.

The Clinical Trials Directive

The Clinical Trials Directive was introduced to implement good clinical practice in the conduct of clinical trials on drugs for human use.⁴⁰ It does not apply, however, to trials for other biomedical products, such as medical devices, leading to uneven protection of research subjects and difficulties in setting up trials.⁴¹ Some Member States, however, enlarged the scope of the Directive in their national legislation and included medical devices in the field of application. Belgium is one of them. The Belgian law concerning experiments on the human person refers to any trial, study or research with an experimental character. It states that the patient's written informed consent is needed to participate in a trial (art. 6).⁴² The information relates to the character, the circumstances, the scope, the targets, the consequences, the expected advantages, the risks linked to the trial, the identification and the advice of an Ethics Committee.

6.2 THE ROLE OF AN ETHICS COMMITTEE

In Belgium, whereas the assessment and agreement by an Ethics Committee is required for the implantation of medical devices within a trial, there is no such requirement for those devices in the experimental phase outside a clinical trial context. Yet, for clinical trials, the Ethics Committee needs to assess several elements that are also relevant to the implantation of high-risk medical devices outside a clinical trial, such as the assessment of the balance between the advantages and the risks for the patient, the aptness of the location, the content of the written information and the procedure to obtain consent (art. 11 § 4).

If, in the future, an Ethics Committee opinion is sought for pre- or post-market clinical trials involving medical devices, it will be important to consider the availability of specific expertise in this domain. This may be difficult to achieve at the level of all Ethics Committees. Interestingly, in the concept paper on the revision of the Clinical Trials Directive, a coordinated assessment procedure (CAP) is considered, whereby joint assessment by the Member States of clinical trials with medicines is stressed.⁴³

Under the CAP, it would be up to each Member State to divide tasks between the Competent Authority and the Ethics Committee. In that scope, it would be an option to grant the task of the risk benefit assessment to the Competent Authority.

6.3 LIABILITY

According to the Directive concerning liability for defective products, a producer is liable for the damage caused by a product defect even without fault.⁴⁴ A product is defective when it does not provide the safety that a person is entitled to expect, taking all circumstances into account, including the presentation of the product, the intended use within a reasonable extent and the time when the product was put into circulation. The problem with the application of this Directive to high-risk medical devices in the experimental phase is that a CE marked device is considered and presented as “safe” for the patient, whereas one could question the level of safety as it was most probably not tested in a controlled trial setting (RCTs are not required for obtaining a CE mark). It is unclear if it is the producer’s responsibility to make sure that the patient is informed of the possible risk of using the device in the experimental phase. Moreover, one of the possible exemptions of liability for the producer is that the state of scientific and technical knowledge at the time of marketing was insufficient to enable discovery of the defect. This is, in principle, mostly the case when giving access to a high-risk medical device in the experimental phase. Consequently, it is doubtful if patients implanted with high-risk medical devices will be able to benefit from this liability system in case of harm.

Although the European Clinical Trials Directive states that provisions need to be made for insurance or indemnity to cover the liability of the investigator or the sponsor (art. 3.2 f), it does not mandate a particular liability system. The concept paper on the revision of the Clinical Trials Directive envisions the policy option to oblige Member States to provide for indemnification for damages incurred during clinical trials performed in their territory.

Today, most of the Member States apply their general liability regime in case of medical errors or negligence in providing healthcare. A few Member States have introduced specific liability rules increasing protection for patients. This implies that citizens of different Member States do not benefit from the same protection regarding potential liability resulting from healthcare interventions. The Belgian law opted to integrate a system of no-fault liability in the Clinical Trials Act. Patients taking part in a clinical trial in Belgium benefit from a no-fault system that rests (or “centralises”) liability with the “sponsor” of the trial if damage is caused by the trial.

In Belgium, no-fault legislation for the compensation of medical harm has been enacted but not yet enforced.⁴⁵ It is doubtful, however, if harm caused by a high-risk medical device in the experimental phase will easily lead to compensation. If harm cannot be compensated via the no-fault system, patients will have to prove a fault in order to get compensation, which is often difficult, costly and time-consuming.

In contrast to the liability dispositions in the clinical trials act, patients benefiting from high-risk medical devices in the experimental phase cannot benefit from any specific dispositions on the centralisation of liability. Yet, it is often unclear as to whom the liability claim needs to be addressed: Is it the manufacturer? Is it the Notified Body who failed to make a proper assessment of the device? Is it the implanting physician, having omitted to make a proper risk assessment even if no guidelines are available or having omitted to inform the patients on the risks?

7 CONCLUSIONS AND RECOMMENDATIONS

7.1 THE LONG-TERM PERSPECTIVE AT THE EUROPEAN LEVEL

Legislative changes needed at the European level

Actions needed for the pre-market demonstration of efficacy and safety

The discrepancy between the European and US situations highlights the need for a significant change in legislation on this side of the Atlantic. FDA considers RCTs are critical for statistical validity. The same agency considers RCTs as ethical if designed according to the US current Good Clinical Practices. In a recent report of the World Health Organisation, regulatory agencies have been called upon to ensure that whenever possible, high quality randomised trials are completed prior to granting marketing approval of high-risk medical devices.²⁶

This is currently not the case in Europe, leading to earlier market introductions compared with the US, at a time when the exploratory clinical development phase is not yet completed and the confirmatory phase has yet to be initiated. Despite the increase in clinical trial activity induced by the EU Directive 2007/47/EC, the remaining variation in the stringency of clinical review both at the level of Notified Bodies and the Competent Authority level is not optimal to guarantee patient safety in a uniform way for EU citizens. The argument that conducting clinical trials is too high a hurdle for small companies lacking clinical expertise and financial support is insufficient when confronted with patients' safety and expectations for effective treatments.

Therefore, for innovative high-risk devices, the future EU Device Directive should move away from requiring "device performance" data only to also require pre-market data that demonstrate "clinical efficacy or effectiveness". The current requirement in the regulation to evaluate the benefit-risk ratio already seems to be in contradiction with the current absence of controlled assessment of clinical benefit (efficacy) and clinical safety. A better standardised high quality review of clinical study protocols and results both at the level of Notified Bodies and Competent Authorities should be realised in order to guarantee patient safety in a more optimal way. Whenever possible, high quality randomised trials can be¹¹ and should be completed prior to granting marketing approval of innovative high-risk devices. This should result in an approved indication for the device. As for medicines, specific regulations are needed for devices aimed at very small target populations.

Instead of trying to streamline a very fragmented system of Notified Bodies and Competent Authorities, a more straightforward way to achieve the goals discussed above could be to centralise expertise. This could be realised under the EMA umbrella, as was done for advanced therapy products. Centralisation of all devices was also suggested by the European Society of Cardiology.¹³ The transfer of evaluation and approval to a centralised body may, however, be more urgent for innovative high-risk devices than for other lower risk devices.

- **For innovative high-risk devices the future EU Device Directive should move away from requiring clinical safety and "performance" data only to also require pre-market data that demonstrate "clinical efficacy".**
- **Competent Authorities and Notified Bodies should ensure that, whenever possible, high quality randomised trials are completed with clinically relevant endpoints prior to granting marketing approval of innovative high-risk devices.**
- **Centralizing the evaluation of high-risk devices at European level might be a viable alternative and should be considered.**

Actions needed to increase the transparency of information

In contrast to the regulation of pharmaceuticals where the EMA makes European Public Assessment Reports (EPARs) public, no document is made public summarising the available clinical data at the time of market introduction of novel high-risk devices in Europe. This lack of transparency and availability of public data makes it impossible for HTA bodies to critically review in detail the clinical data sets used to obtain CE marking. Also, physicians can only practice evidence-based medicine and patients can only make an informed judgment if all available clinical study results are made public in a transparent way.

This lack of transparency may explain why, in contrast to the situation in the US, patient safety aspects of the European approach for high-risk devices have not been widely discussed in peer reviewed journals. This trend was reversed during the finalisation of this report with the publication of a series of articles on European medical device regulations in the *British Medical Journal*^{1, 2, 10-12}. The main message is the same as in this report: “the regulation is in need of a major overhaul”.² Also, a policy report by the European Society of Cardiology was published.¹³ It includes a number of recommendations for the EU Commission which are mostly in line with those formulated in our report, with respect to the need for transparency and standardisation of device evaluations.

For pharmaceuticals, HTA agencies in collaboration with the EMA have tried to obtain access to more complete sets of (unpublished) clinical trial results. The EU Clinical Trials Register now also provides protocol-related information to the public, but only for trials with medicines. Similar initiatives may need to be developed for novel high-risk medical devices in Europe. In the US, since 2007 full transparency is assured by the obligatory registration of trial protocols and study results, both for drugs and devices.⁴⁶ HTA agencies should at least have access to the obligatory registry of device clinical trials (EUDAMED). Regulatory agencies should ensure that all the results of all conducted studies are made available to HTA agencies and to the public, as is the case in the US.

- **The new pre-market procedure should result in an approved indication for the device and a publicly available product documentation including the full results of all trials. This transparency is required to allow physicians to practice evidence-based medicine, patients to make an informed decision and HTA agencies to produce the correct assessment.**

The need for harmonised guidance for pre-market clinical trials and the role of HTA agencies

Ideally, European HTA agencies should jointly prepare an algorithm which clearly describes the clinical evidence that is necessary for a meaningful evaluation. For pharmaceuticals, HTA agencies in collaboration with the EMA are already exploring ways to provide input during clinical development.

A stronger harmonisation of pre-marketing requirements for clinical trials between regions of the world should be the aim for innovative high-risk devices. In this regard, initiatives to develop international guidance documents for the pre-market clinical trials by type of high-risk device need to be stimulated.¹² Such guidance documents have proven to be of value for more standardised high quality clinical development of medicinal products. Not only professional societies¹³ but, ideally, HTA agencies should also be involved in this activity, e.g. proposing study endpoints that will be needed for cost-effectiveness evaluations. Such documents should also further the standardisation of evaluations across Notified Bodies and Competent Authorities.

- **European HTA agencies may consider jointly preparing an algorithm which clearly describes the clinical evidence necessary for a meaningful evaluation of innovative high-risk devices.**
- **Guidance documents for pre-market clinical trials by type of high-risk device need to be developed. HTA agencies should also be involved in this activity.**

Implications for the payers

Payers will be more willing to cover expensive innovative devices if they have proven their added value in terms of clinical efficacy in a comparative trial with the standard of care.

In the US, the US Centers for Medicare and Medicaid Services (CMS) will reimburse the cost of medical devices studied in the pre-market setting if they meet certain criteria. The level of reimbursement is up to the cost of a currently marketed, similar product. In order to lower the financial hurdle, payers in Europe should also consider such co-financing of innovative high-risk devices used in pre-market clinical trials, provided these trials are well-controlled and have clinically relevant endpoints. As payers and systems in Europe differ considerably by Member State, it is more complex to realise such co-financing compared with the US.

- **Payers in Europe should consider, as is the case in the US, co-financing of innovative high-risk devices used in pre-market clinical trials.**

Implications for the industry

What could be the consequences for industry if Europe moves away from requiring “performance” data only to also requiring pre-market data that demonstrate “clinical efficacy” for innovative high-risk devices?

Industry could benefit if a positive reimbursement can be better planned, and if potential liability risks of too-early market entry can be reduced. Smaller engineering-based device companies should be made aware of the growing importance of generating clinical evidence and the specific expertise required.

Companies would see a delay in market introduction in Europe for innovative high-risk devices and potential sales lost. However, as payers become less willing to pay in absence of efficacy data, these sales might be lower than expected anyway.

Manufacturers who try to introduce an innovative high-risk device also on the US market already plan the RCT investment today. As discussed above, payers in Europe should consider, as is the case in the US, co-financing of innovative high-risk devices used in pre-market clinical trials.

- **The device industry should be made aware of the growing importance of generating clinical evidence and the specific expertise this requires.**

Implications for the patient

For the patient, the current system in Europe can mean earlier access to a potentially lifesaving device, but at the risk of insufficiently documented efficacy and potential safety issues. Even excess mortality cannot be excluded as the clinical evaluation of the device is often very limited at that stage and not made public.

If the recommendations are implemented, more evidence on safety and efficacy would be publicly available at the time of market introduction. This should result in better informed decision making by the physician and the patient.

Patients should be adequately informed of the possibility of participating in pre-market clinical trials of innovative high-risk devices. In such a setting, full patient information and written patient informed consent should be the rule.

A more complete clinical evaluation in the pre-market phase will reduce the risk for the patient, not eliminate it. Post-market surveillance will remain necessary to detect infrequent or long-term complications.

- **Patients should be explained that a more complete clinical evaluation in the pre-market phase will reduce the risk but not eliminate it.**

7.2 TRANSIENT SOLUTIONS AT MEMBER STATE LEVEL

Awaiting a reworked Medical Device Directive in Europe, the responsibility for demonstrating clinical efficacy and further document patient safety (after marketing) is left to the marketing company, medical societies and hospital directors. At least in Belgium, hospitals may want to advertise the early adoption of innovative devices on their website, inducing other hospitals to follow their example. Awaiting inclusion of the device in the list of reimbursed devices, patients may be charged an important co-payment although the use of the new device may not be the best choice in terms of patient safety and efficacy.

The hypothesis that manufacturers generate a higher level of clinical evidence than that required by the regulators is unrealistic.¹⁵ Depending on the local policy of the company and the Member State, novel high-risk medical devices may or may not be introduced first in selected experienced centres. Such controlled introduction of high-risk innovative devices can be stimulated by programmes (trials, often patient registries) of conditional reimbursement with evidence gathering, as is being implemented in France. However, such initiatives do not prevent the sales and use of the device beyond the trial setting, with patients being fully charged for the device. Unless the company strictly controls this market introduction, the expertise of the physicians using the high-risk device may vary considerably between Member States and potentially put the uninformed patient at risk.

With regard to patient safety of medical devices, the major control point in Europe is post-marketing surveillance rather than pre-marketing as is the case for medicines.³ Post-market surveillance is, however, hampered by an ongoing struggle with both under-reporting of the numerator (the number of adverse events) and a lack of data about the denominator (the total number of exposures).²¹ These numbers are also lacking for devices.¹ Without active analysis, this important control point often remains an empty shell and a false reassurance of patient safety. In this context, it has been reported that many manufacturers fail to fully fulfil their legal responsibility to collect product data once their device is on the market.¹⁰ The industry statement that no information is available to suggest that patient safety in Europe has been compromised may thus need to be interpreted with caution.¹⁰

- **Awaiting a reworked Medical Device Directive, patient risk should be minimised at the Member State level by improving transparency with regard to the available clinical data and by limiting the market introduction of novel high-risk devices with minimal clinical data to centers with the necessary expertise. Preferably, this should be done under an appropriate research protocol (RCT if possible). This requires the commitment of the Competent Authorities, the marketing company, the physicians and the hospitals.**
- **The ethical issues associated with the early market introduction of innovative high-risk devices should be studied further by the commissions and organisations that provide ethical guidance to the physicians and hospitals.**

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