



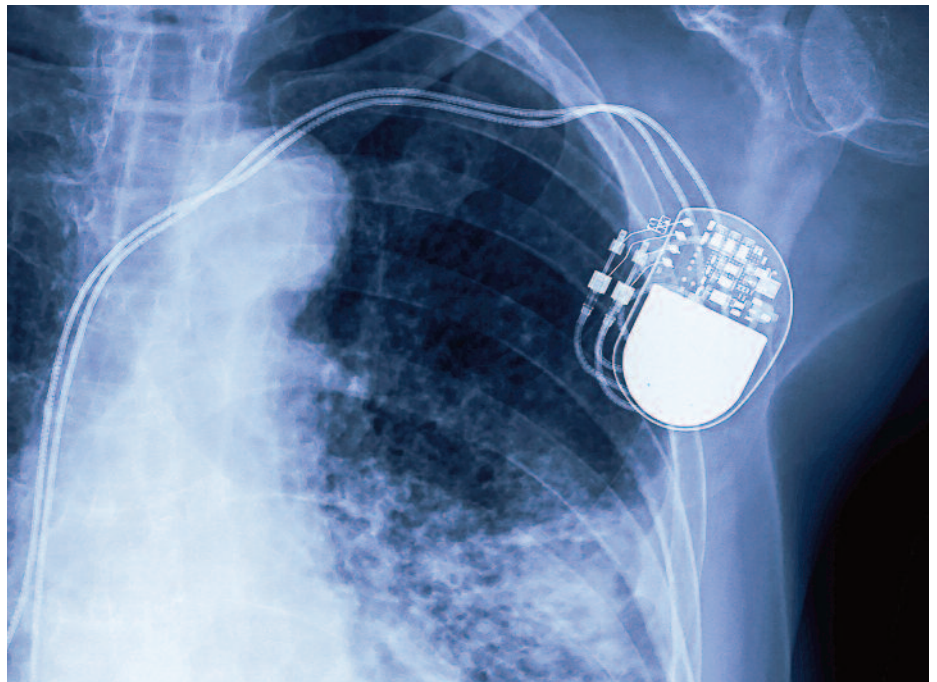
The next medical device scandal: Medical device files – my personal view (Part 2)

In the last issue, I started to share my opinion on the recently published “implant files”.^{1,2} As this topic could be discussed endlessly, I focused on an article in a German newspaper, the *Süddeutsche Zeitung*, that provided a summary about the “10 facts to know about the implant files”.³ In Part 1,² the first five “facts” were discussed, and this part will focus on the remaining assertions, which are indicated in the subheadings below.

“Frequently, devices are implanted that are not or barely tested”

The article reported that patients do not know how an implant has been certified and that the majority of implants are introduced to Europe without premarket clinical studies. Medical device approval is theoretically possible through the principal of equivalence and clinical studies can be avoided in cases where similar or “equivalent” products are already available on the market. From 2020 onwards, manufacturers can only submit CE dossiers for equivalent devices if they have the same information for the equivalent device that the manufacturer has and explain how and why it is equivalent. But the loophole remains in effect and new devices, if approved, can be sold without being clinically tested in humans.

As stated in my last article,² it is true that approval to distribute a device (“CE-certification”) has in the past often been based on limited clinical data. This is one of the reasons why the new, more rigorous device regulations were developed. Clinical Evaluation Guidelines (MEDDEV 2.7/1 revision 4) were published in June 2016 and the Medical Device Regulation (MDR 2017/745) was published in May 2017 (and will be in full effect after a 3-year transition period starting in May 2020). Both documents add new levels of



scrutiny and demand more clinical data for CE-certification and post approval data for CE-mark retention and renewal. Of note, the intensification/expansion of the equivalence approach is already in force as this was modified in the MEDDEV 2.7/1 rev 4 (June 2016) criteria.

The new MDR will require that clinical study reports be published and made available to the public (together with a lay summary), so that patients and interested parties can be informed about the clinical study results that led to CE-certification. Rather than reporting shortcomings of the past which have been amended – the authors of the implant files should have informed the readers about this prospective opportunity.

So, in short, this section of the article talks about a past situation that has changed since MEDDEV 2.7/1 Rev 4 and which will further improve once the MDR 2017/745 is fully

applicable. Regarding the still existing CE approval loophole: Yes, in rare circumstances, the equivalence approach can still be used to obtain CE-certification, because sometimes it indeed makes sense, e.g., if the product changes are only minor, can be sufficiently evaluated using preclinical data, and with planned formal post approval follow-up studies, particularly in low to medium risk devices.

Most of the studies are financed by the industry

The report states that even if there are studies, they are barely independent. Frequently authors have financial relations to the manufacturer of the devices. Furthermore, most of the studies are funded by the industry. And physicians say that studies that are negative “disappear”.

The sentence “even if there are studies” implies

that there are barely any studies, which is no longer the case. Meanwhile, for innovative, high risk devices, it is nearly impossible to receive CE-certification without data from clinical studies.

Related to financial interest: It is true that many clinical investigators may have a financial relationship to the manufacturer of the device, but:

- This must be declared in medical society presentations or publications as a “conflict of interest statement”.
- Furthermore, in clinical investigations (syn. clinical studies) investigators have to disclose any conflict of interest, e.g., using a “financial disclosure form”.⁴ These forms are commonly submitted to the ethic committees and competent authorities along with other professional details of the investigators. If an investigator has declared such an interest, it needs to be justified as to why this does not influence his participation in the clinical study.
- Financial contracts for clinical studies are commonly negotiated with the institution, as it is not allowed to directly pay investigators in most of the European countries.
- Notably, only the work performed is allowed to be reimbursed and the payments need to reflect “fair market value”.
- In most European countries financial contracts for clinical studies are supervised at a national or local institutional level. For example, in France, the Conseil National de l’Ordre des Médecins (CNOM, French Medical Council) needs to review and approve each contract between the industry, investigators, and all other involved health care professionals prior to study commencement at the investigation site. Furthermore, in most European countries, relevant parts of the contract (such as payment details) need to be submitted along with the study application to the competent authority.
- In relevant clinical studies leading to CE-certification, separate contracts are often made with independent data safety monitoring boards, clinical event review committees, and core laboratories, adding another level of independency. Of course, in the end, those committees are paid by the sponsor for the services they render, but in my experience, they are well aware of their responsibility.

Unfortunately, the authors neglected to inform the readers about positive developments such as the US⁵ Sunshine Act, which also appears to be implemented in some form in the pharmaceutical industry.⁶ Although there has been no pan-European Union agreement on the

appropriate standards of transparent payment disclosures, many EU member states have enacted Sunshine Act provisions including France, Portugal, Belgium, United Kingdom, Denmark, Romania, Latvia, Turkey, Slovakia, and Greece. Anticorruption/transparency laws are also in place in Croatia, The Netherlands, Germany, Italy, Poland, Slovenia, Sweden, and Spain.⁷⁻⁹

The statement that the majority of studies are funded by the industry is true. But for premarket and mandated postmarket studies, this is not voluntary. I can imagine that companies, particularly small start-ups who depend on external funding, would welcome someone else paying for their premarket trials which generally cost several million Euros. For postmarket registries, it is already common to have national registries, e.g., for transcatheter implantation the FRANCE registry,¹⁰ the TVT registry in the US,¹¹ the GARY registry in Germany,¹² or for stent placement the Scandinavian SCAAR registry.¹³ In addition to the current national registries, article 108 of MDR2017/745¹⁴ encourages the use of registers and databanks that shall contribute to the independent device evaluation, so it is expected to see even more in the future. Notably, these registries frequently have poor follow-up compliance as it takes tremendous efforts and very thorough study oversight to ensure good follow-up compliance, so a mix of manufacturer initiated and national registries may be a good future post market data collection scenario.

That studies with negative results disappear is a statement that I do not agree with from my experience. To be published in peer-reviewed journals, medical device clinical trials must be posted on platforms such as clinicaltrials.gov and both positive and/or negative outcomes have to be published. Approximately 2 years ago, there was some discussion that only around 50% of studies were reported, but it turned out that the analysis algorithm only identified studies as being reported if the associated clinicaltrials.gov number was displayed in the abstract or method section and that many more studies have in fact, been reported.

Also, anyone who has been involved in publication knows how difficult it is to have negative results published (unless it is something truly relevant with clinical consequences). Journal editorial committees are interested in maintaining their readership with clinically relevant results. In my personal experience, the trial with the least interesting results, e.g., a trial that reported no difference between the groups (hence negative for the study sponsor), required submissions to at least five different journals and

took more than 2 years to get published.¹⁵

Unfortunately, the reporters missed the opportunity to inform the reader that trial results are available on clinicaltrials.gov (where results can be posted in case they are not published or where a link to the respective publication should be posted). Furthermore, from 2020 onwards, the MDR-requested database should be in place and clinical study results can be accessed there.

If something goes wrong, the patient often is not informed about it

This has been true in the past, has been identified, and the new MDR 2017/745¹⁴ intends to fix this situation. Through the EUDAMED (European Database on Medical Devices) database, relevant information about a device will be centralised. Information about device certification, clinical studies and lay summaries, clinical study reports or summary of safety and performance of implantable class III devices will be accessible (see article 33 MDR2017/745 for further details). Moreover, for implantable devices, patient implant cards need to include a link to the manufacturers website that will need to contain current product information in lay terms (see article 18 of MDR2017/745 for further details).

So, this statement refers to the past, will likely be resolved soon, and again fails to provide the reader about options to obtain information.

Regulatory authorities rarely react

In Germany, neither the Federal Ministry of Health nor the competent authority BfArM provided the information about which product has caused most deaths in the past 10 years as they claim these are “confidential information”.

Frankly speaking, the information about which product has caused most deaths in the past 10 years is irrelevant. As detailed in Part 1, a device relationship is already claimed as soon as a relationship cannot be reasonably excluded. With this, the number of “device-related deaths” also correlates with the existing patient comorbidities. For instance, in the aortic transcatheter PARTNER US study,¹⁶ 19.6% of patients that were classified as high risk and inoperable died from cardiovascular causes within one year. This sounds like a very high rate of death however, the randomised comparator group that received standard therapy (medical therapy) had a 1-year mortality of 41.9%. Everything has to be seen in context.

Regulatory authorities rely on the fact that in case of failure, the manufacturer recall their device or provide safety warnings. Since 2010, this occurred

around 10,000 times, but there were only 6 recalls from the authorities during this time.

These numbers seem to show that the majority of medical device companies take their responsibility for patient safety and device quality very seriously. Furthermore, it is logical that manufacturer recalls are higher than recalls from the regulatory authorities for the following reasons:

- Companies know their product best and usually receive the relevant information first, therefore it is logical that they start the recalls first.
- There are frequent actions and “prophylactic” recalls initiated by companies before something happens.
- A company can freely recall their device whenever they want, but the competent authorities need to provide a respective justification.

As stated in Part 1, there is still room for improvement for notifications of incidents outside of clinical studies, but this is not in the hands of manufacturers or notified bodies, but those who should report those events (mostly physicians). Patients themselves have the option to report such incidents to the competent authorities, but are frequently not aware of it. Sadly, the opportunity to inform the readers about this option was missed.

The medical device lobby is blocking changes

The European Commission and parts of the European Parliament wanted to implement stricter rules since years, but there was no change in the system despite year-long negotiations. Still private notified bodies instead of national authorities decide over the certification of new medical devices. If the device is useful does not need to be proven.

In 2012, based on the discovery of the fraudulent use of non-medical grade silicone in breast implant, the European Commission called for “immediate actions – tighten controls, increase surveillance, restore confidence”.¹⁷ Only 4 years later, MEDDEV 2.7/1 revision 4 was released with stricter requirements, and the more comprehensive MDR¹⁴ has been released in 2017, which will be fully applicable in 2020.

Regarding notified bodies as private entities: As I already explained in Part 1, notified bodies cannot act in a legal vacuum. The national authority is responsible for setting up and carrying out the necessary procedures for the assessment and designation of conformity assessment bodies under a Mutual Recognition

Agreement (MRA) or under the CETA Protocol on Conformity Assessment. Furthermore, independent Expert Panels under the supervision of the European Commission are involved in the review of class III and implantable devices. Whoever is interested, can read MDR Annex VII¹⁴ “Requirements to be met by notified bodies”.

That it does not need to be proven that the device is useful is incorrect. MEDDEV 2.7/1 rev 4 has strengthened the necessary justifications to show that the device is a safe state of the art device including extensive material and function tests as well as a specific literature search.

Summary

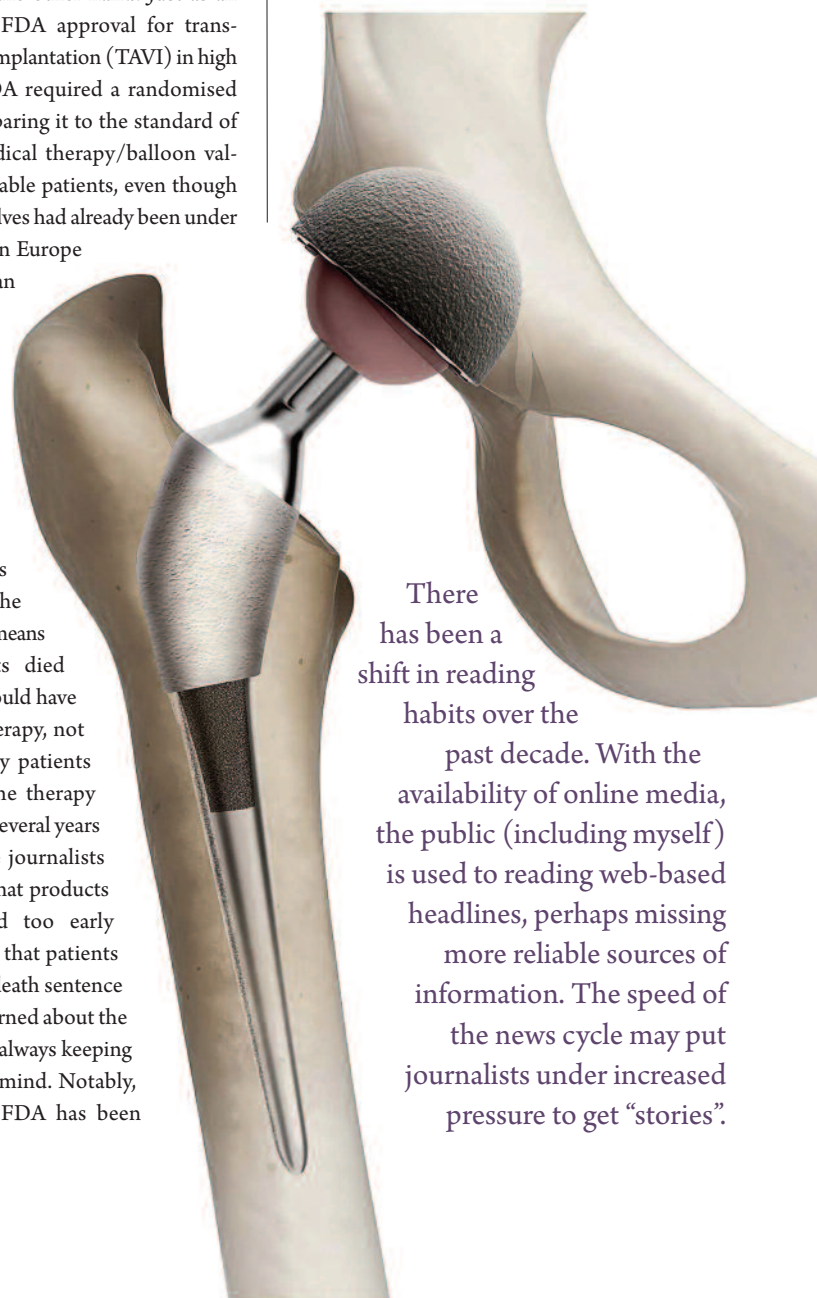
In general, it is important to understand that it is impossible to find the perfect balance between product safety/security and innovation. Previously, the US was stricter than Europe. While that led to increased security and fewer events for patients on one hand, it led to a delay in life-saving therapies on the other hand. Just as an example, to obtain FDA approval for transcatheter aortic valve implantation (TAVI) in high risk patients, the FDA required a randomised controlled trial comparing it to the standard of care, which was medical therapy/balloon valvuloplasty for inoperable patients, even though transcatheter heart valves had already been under study and approved in Europe and large European registries had been initiated, which means a substantial amount of clinical data was available. In the US-trial, the 1-year mortality in the comparator group was 20% higher than in the TAVI-group,¹⁶ which means that several patients died even though there would have been an adequate therapy, not to speak of the many patients who died because the therapy was not available for several years in the US. The same journalists who now complain that products have been provided too early would have reported that patients are randomised to a death sentence if they would have learned about the situation in the US – always keeping a selling headline in mind. Notably, since then, the US FDA has been

working on a new process facilitating the introduction of innovative medical devices.¹⁸

The journalists also cite physicians that have concerns regarding industry. During my career, I also came across such physicians. However, having a strong business acumen, I always had the opinion that – the sooner I know about a potential problem – the sooner I can fix it, hence preventing potential (financial) harm. Building a best-in-class product through thorough oversight is the best assurance for profit.

To conclude, it is important that journalists and other people critically assess and challenge the status quo. However, just hunting for headlines and biased reporting is a missed opportunity. As a reader, I want to be provided with facts and want to develop my own opinions rather than being fed the opinions of others. Worst is that opportunities to inform the public about sources of reliable information have been missed.

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the past decade. With the availability of online media, the public (including myself) is used to reading web-based headlines, perhaps missing more reliable sources of information. The speed of the news cycle may put journalists under increased pressure to get “stories”. While I do not know how to change this in the future, I do hope that we will find a way back to balanced reporting.

Whoever is interested in further reading can access an interesting executive summary of an interview with Bernasconi, MedTech Europe, at <https://bit.ly/2F51HsT>.

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Conflict of Interest

The author acts as a medical writer and consultant in the medical device industry and owns shares in Edwards Lifesciences.

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