

New regulations for medical devices: Rationale, advances and impact on research and patient care

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Abstract

A series of events relating to inferior medical devices has brought about changes in the legal requirements regarding quality control on the part of regulators. Apart from clinical studies, register and routine data will play an essential role in this context. To ensure adequate use of these data, adapted methodologies are required as register data in fact represent a new scientific entity. For the interpretation of register and routine data several limitations of published data should be taken into account. In many cases essential parameters of study cohorts - such as age, comorbidities, the patients' risk profiles or the hospital profile - are not presented. Required data and evaluation procedures differ significantly, for example, between hip and spine implants. A "one fits for all" methodology is quite unlikely to exist and vigorous efforts will be required to develop suitable standards in the next future. The new legislation will affect all high-risk products, besides joint implants also contact lenses, cardiac pacemakers or stents, for example, the new regulations can markedly enhance product quality monitoring. Register data and clinical studies should not be considered as competitors, they complement each other when used responsibly. In the future follow-up studies should increasingly focus on specific questions, while global follow-up investigations regarding product complication rates and surgical methods will increasingly be covered by registers.

Key words: Arthroplasty; Outcome; Research; Medical device; Regulation

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Core tip: In the next few years new worldwide regulations as well as the availability of register data will

lead to a shift in scientific focuses. The interpretation of register and routine data will be associated with new methodological challenges. Monocenter follow-up studies will become less attractive. Publications based on large data sets from registers will continue to gain influence and cover general issues; clinical studies should focus on specific questions.

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INTRODUCTION

Arthroplasty is one of the most successful interventions in terms of gain in quality of life^[1]. Nevertheless we must acknowledge the fact that about one in ten patients have to undergo revision surgery in the course of their life^[2]. Increasing age and the patients' growing confidence in the success of the operation are leading to rising numbers of cases. Moreover, patients are treated at an ever younger age, and even older patients increase their physical activity - and thus the strain on the implant. As a consequence, a marked future rise in revision surgeries has to be expected^[3].

Incidents with inferior products occurred at regular intervals in the past, with a significant number of patients harmed and great cost incurred by the healthcare system due to the necessity of revision surgeries. ASRTM and other metal-on-metal large diameter head implants, 3MTM hip system or cemented titanium stems are only a few examples^[4,5]. These problems are by no means restricted to joint implants only, but affect all groups of high-risk products, such as osteosynthesis devices, breast implants, contact lenses or cardiology products^[6-9]. It should therefore not come as a surprise that regulatory bodies like Food and Drug Administration or European Union Commission have taken initiatives to improve the situation as a whole, provide a higher level of safety to patients and physicians, and apart from personal suffering also reduce expenses in healthcare.

The experience of the past few years has shown that technical assessment, as well as the standard practice to evaluate outcome quality and potential risks of medical devices by means of sample-based clinical studies are insufficient^[10-12]. This is mainly due to some basic-medical device-specific-conditions, as well as to general structural weaknesses in the scientific system and the current evaluation procedures.

Limitations of the present system

Any of the current procedures is based on a standardized rating system for clinical evidence and studies with prospective randomized controlled Trials (RCT) considered as best study design. These standards pri-

marily take account of the circumstances that apply to pharmaceuticals. White tablets in anonymous boxes can easily be used in controlled and randomized circumstances; biological half-life allows a good estimate of the period of examination during which side effects have to be expected; persons collecting data can easily be blinded.

When it comes to implanted medical devices, this scheme reaches its limits. It is difficult to randomize surgical procedures, in many cases impossible due to ethical reasons. Placebo groups are unethical in general. Blinding of the physician who makes the decision and is responsible for documenting the study endpoint is hardly possible. For the standard endpoint Revision Rate this would, for instance, mean that the surgeon who decides on revision surgery and performs the intervention would neither be granted access to patient records nor to X-rays.

These limitations might be one reason for the low numbers of RCT's in orthopaedics. Since it is virtually impossible to estimate the time at which a complication occurs, the times for follow-up examinations and the duration of the study can hardly be determined prospectively. For example, if the lifespan of the battery of a pacemaker is three years, the problem would not be realized in a one-year study; at 5 years follow-up two years would have passed until measures can be taken - with patients being treated with a suboptimal product in the meantime. The logical approach of regular concomitant check-ups carries the risk of bias due to a break of the blinding and impact on the assessment of findings by discussing the evaluations performed; the methodological benefits of prospective study design would seriously be put into question.

Regardless of these limitations a systematic analysis of published results in regular clinical studies as compared to register data has revealed profound structural weaknesses in the current science system. About half of the implants examined in this worldwide meta-analysis of clinical studies showed statistically significant deviations of over 300% (as a measure of relevance in which deviations might also be explained by other factors, such as patient selection or the surgeon's expertise) compared with national register data as a measure for average patient care. Especially studies from the United States, as well as studies authored by implant developers were conspicuously often affected by implausibly good results. Marked differences were also found as to what was published in journals, for example, that on average 55% of cases published in orthopedic United States journals stem from implant developers, compared to only 7.5% in European journals^[13]. We must therefore accept that the present standards in scientific activities are susceptible to stakeholder influence, with a substantial impact on the opinion of orthopedic literature.

In principle the current standard of assessment gives very limited consideration to clinical studies. The primary objective of this assessment scheme is to restrict methodological shortcomings of sample-based studies. However, the concept neither gives full consideration

to the complete registration of all cases, as is largely achieved in good registers, nor does it allow for the specific requirements outlined above. Thus, a prospective randomized study of 50 patients would have to be classified as superior to a register evaluation of 50000 cases. Owing to the high standard in patient care, the endpoints of orthopedic studies, such as revision rate, are relatively rare. L.I. Havelin, one of the major co-founders of the Norwegian Arthroplasty Register, proved in his PhD thesis that in a conventional follow-up study nearly 15000 cases would be needed to determine a difference of 1 percentage point in the complication rate after 10 years. The relatively big effect of 2 percentage points would still require about 3000 patients. Therefore, the vast majority of published studies have to be considered as statistically underpowered, even if they are impeccable from a methodological point of view. In the 2010 comparative analysis of published clinical studies worldwide and the restricted number of high-quality national registers 80% of all cases available came from registers, only 20% from clinical studies^[13]. Now, five years later, the ratio has shifted to 90:10 percent. Considering that the National Joint Registry of England, Wales and Northern Ireland records more than 200000 cases per year, it is reasonable to assume that this data source will become increasingly important in the future.

Advances in future regulations and new challenges

In addition to a comprehensive presentation of all outcome quality data available, future legislation will also require a performance estimate within the scope of average patient care. This is supposed to address the problems associated with the fact that clinical studies are often conducted in centers of excellence, which are not representative for average use.

Improved monitoring shall include the product's entire lifetime, which can de facto only be covered by registers. Indicators for measuring embrace the whole treatment chain. Revision rate, the most important indicator for arthroplasty, in addition to product quality for example also includes the surgeon's quality, the patient's risk profile or general conditions of a healthcare system. Attribution of inferior outcome to a causer will be an essential factor as it defines at which stakeholder improvement measures can be launched. It is expected that this point will be an issue of controversial debate, particularly since responsibilities will be shared in many cases and serious legal and financial consequences may be involved. In the necessary decision-making process previous experience from register practice so far will be only of limited use. In past years and decades the interpretation of scientific data was largely a preserve of physicians. The data were published at congresses or in journal articles; that way critical debate was initiated within the expert audience, and physicians as the main decision-makers were expected to draw the consequences. Under these circumstances it makes sense to take action as early as a relevant problem is suspected. Regulators, authorities

or manufacturers, however, are bound to make clear and unambiguous decisions, such as recalling a product from the market - or not. This requires a higher level of reliability with regard to conclusions than is necessary for the discussion among experts. To ensure that the future procedures can actually meet the objectives of safety improvement, a number of issues have to be dealt with.

Issues to be addressed

Registers in principle are a new scientific entity which imposes special requirements on data collection and evaluation. One could compare the published annual reports, in some cases also journal publications, to clinical studies without "Materials and Methods". The patient cohorts included often are not or only insufficiently described, which may also be explained by the fact that the evaluations are chiefly addressed to physicians and other stakeholders of the respective country - who are usually familiar with the local circumstances. As the results are primarily intended for implementation in this particular area, the circumstances represent a constant and are therefore less important than for those readers who would like to apply the findings to other countries.

Even within the European Union the results of interventions show relevant differences in the population. Life expectancy, for instance, is about 10 years lower in some countries, such as Romania, than it is in Central European countries, or compared to Australia, for example, since the "positive outcome" of arthroplasty interventions effectively is the patient's death for another reason without the implant being revised, this is more probable for a 70-year-old Romanian than for a German, British or Australian of the same age. Therefore, registered differences in revision rate cannot be automatically interpreted as differences in the quality of treatment. The definition of relevant parameters for the final outcome and a structured description of the respective dataset would be useful to enable the reader to check whether the conclusions of a foreign register can be transferred to his or her own conditions.

Furthermore, the effects of the individual parameters should be quantified, which would be possible by comparative analyses of existing register datasets. The ultimate aim should be the standardization of data collection and evaluation procedures, at least when data from different registers are aggregated.

This can only be realized through international, if possible world-wide cooperation of registers, regulators, as well as the other stakeholders involved. Moreover, it would make sense to include the users of the data such as physicians and - beyond the narrow circle of register experts - product manufacturers or patients' mandatories. Open, transparent and democratic processes are of vital importance to ensure that the solutions to be elaborated receive social acceptance. As the results will have great influence on far-reaching decisions in patient care, careful and critical evaluation practice is a necessity. Risk adjustment regarding individual

factors and confounders is essential in the analysis of aggregated international data.

When going through foreign register data one should critically examine whether the results and conclusions could be affected by confounders and whether the basic data are representative for one's own area.

Future legislation is supposed to apply to all high-risk products. However, the pathologies, circumstances and aims these will be used for will vary greatly. Apart from joint implants, the range of products concerned also includes all permanently implanted orthopaedic devices, contact lenses, pacemakers, artificial cardiac valves or stents.

This inhomogeneity certainly has an impact on the evaluation and interpretation of the data, as well as on the conclusions drawn. Arthroplasty has acquired a leading position with regard to registers, not least because of favourable circumstances. The demand that no revision surgery should be required in the course of a patient's life after arthroplasty implantation is the basis for quality measurement. Any serious problem of or around the implant usually leads to revision surgery - which by definition is the "undesirable side effect" of the intervention. The procedure is performed in a hospital; comprehensive documentation is available for evaluations. Similar circumstances are true for a whole series of other medical devices, such as contact lenses, breast implants or pacemakers, but not for all. For a number of products, such as cardiac stents, mortality is the primary endpoint - and death may, but does not have to be associated with the use of a certain product. The removal of osteosynthesis devices or extension of a spinal fusion is not necessarily an undesired consequence of a primary intervention of insufficient quality. In the case of some products, for example, in shoulder and ankle arthroplasty, there are numerous patients who, in spite of unsatisfactory outcome, do not receive revision surgery. Thus, the endpoint of revision rate is meaningful only to a limited extent. In the future it will therefore be necessary to develop optimal solutions for every situation, "one fits for all" will hardly work.

Effects on patient care and science

The possibilities offered by the growing penetration of information technology in our working environment IT will lead to a rapid increase in routine data available. These provide a much better reflection of the reality of patient care than many clinical studies ever could since they are based on clearly defined patients and carried out by experienced surgeons under the favorable circumstances of centers of excellence. However, as medicine is anything but standardized - and presumably can hardly be standardized owing to the variability of patients and medical care - the transferability of results remains a relevant problem inherent to the system. Big data will become increasingly important in all our efforts to improve the quality of our services. Just like

in other areas of electronic data growing quantity does not automatically mean better quality. However, if dealt with and used critically, they open up new possibilities. In the process, certain study designs may become less important, such as simple follow-up studies with minor cohorts of a few hundred patients. The knowledge gained will hardly be able to compare favorably with register data and the usually considerably larger numbers of cases. Register evaluations, on the other hand, can only convey a relatively rough outline; the examination of detailed questions or treatment options will remain a domain of clinical studies. The cooperation of these two scientific tools can create added value, for example, when register data are used to adjust control groups more precisely. As many conventional follow-up studies are at present conducted for the purpose of the post-marketing clinical follow-up of products, it is likely that it will be less economic for implant manufacturers in the future to keep supporting this tool with the resources currently available. It is to be anticipated that budgets will be reallocated to registers on the one hand and clearly focussed clinical studies on the other hand in order to meet the requirements on the part of authorities and regulators. Most likely this will affect the way of implant development and acquisition of clinical evidence. Registries open opportunities for improvement by continuous feedback and outcome monitoring for manufacturers and implant designers. To assess detailed issues experimental, biomechanical and clinical studies will be essential, in premarket test phases as well as innovation circles.

CONCLUSION

Amended legislation in the quality assurance and monitoring of medical devices will allow for a marked improvement in patient safety and the quality of medical care. However, a number of methodological fundamentals for scientific assessment are still to be elaborated. While routine and register data are an increasingly important source of information, they will by no means supersede clinical studies but rather complement them. The time frames of scientific studies in orthopedics are often long; one should consider to make the necessary adjustments to the future situation now.

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