MENTORS IN ORTHOPEDICS

REGISTRIES AND THE NEW EU MEDICAL DEVICE REGULATION: IMPACT ON PATIENT CARE, PRODUCT DEVELOPMENT, FINANCIAL SUPPORT AND RESEARCH

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SUMMARY

Background: The transition from the Medical Device Directive (MDD) to the Medical Device Regulation (MDR) in the European Union addresses historical failures in identifying suboptimal orthopedic implants. Previous reliance on sample-based clinical studies often failed to detect high revision rates in devices such as the ASR hip system until significant patient harm occurred. Structural biases and insufficient statistical power in published literature have historically delayed the identification of device-related incidents.

Objective: This article evaluates the regulatory shift toward the MDR, focusing on the integration of real-world evidence and registry data to enhance the monitoring of safety and performance in orthopedic arthroplasty.

Key Points: The MDR mandates systematic reviews and the utilization of registries, broadly defined to include national quality databases, institutional records, and manufacturer-led observational systems. Unlike traditional clinical trials that prioritize internal validity, registries offer superior external validity by reflecting average clinical practice. Manufacturers are now legally required to perform annual clinical evaluations for high-risk devices, utilizing representative market samples. This regulatory evolution necessitates more rigorous pre-market testing and continuous post-market surveillance, shifting the research landscape from isolated expert-center studies toward professionalized data extraction and large-scale correlation analysis.

Conclusion: The implementation of the MDR transforms orthopedic device development and research by prioritizing longitudinal registry data over short-term follow-up studies. This framework aims to improve patient safety through transparent clinical evaluation reports and proactive identification of implant deficiencies, requiring increased cooperation between manufacturers, surgeons, and healthcare institutions.

KEYWORDS

Arthroplasty, Replacement, Hip; Device Approval; Registries; European Union; Equipment Safety

INTRODUCTION

Medical Devices are a highly regulated business. Manufacturers are in charge by law to provide devices to users and patients, which are safe and perform as intended (1). They have to provide evidence on that to regulatory bodies. Notified Bodies are the main operative regulatory institutions. They grant the CE-certificates, which allow market access for medical devices in the entire common EU market. They act under supervision of competent authorities by all EU member states and the EU Commission.

To identify potential problems with devices a wide range of instruments has to be implemented according to the present legal frame work, the Medical Device Directive MDD (1). Implants have to be tested extensively during design and development, after marketing potential incidents have to be reported and analysed, risk management have to be implemented for any devices over the entire life time and studies have to be conducted to collect clinical data on the device during patient treatment. These studies are at present a major source for grants supporting research activities.

Nevertheless, the history of arthroplasty shows a series of incidents as almost any other type of medical devices. ASR hip and similar large diameter metal on metal heads or 3M Capital Hip are 2 examples. (2,3). Thousands of patients had to be revised due to device related problems, public health care systems and manufacturers had to cover significant costs. One might argue with good rational why a comprehensive legal system, significant investments by manufacturers in quality of their products and thousands of expert users were not able to detect such incidents earlier.

This article is a summary presentation based on experience of 15 years as researcher, supporting expert to the EU Commission during development of Medical Device Regulation and related Guidance Documents and working as clinical reviewer and in a management position for a Notified Body on the implementation. The article is focused on the subject of registries, wider scopes are adressed in other publications. (12, 13)

THE MEDICAL DEVICE DIRECTIVE (MDD)

A critical review on the processes applied since the Medical Device Directive was implemented almost 25 years ago is useful. At this time, there was almost no comuter on hospital wards, documentation was based on paper, both for routine care and research. Consequently, only a small part of patients using a specific device was accessible for monitoring of safety and performance. Special interest groups like manufacturers and related researchers were able to create confounders in scientific evidence. (4, 5, 6). Certainly, this did not affect the entire range of evidence, however there are signals for structural bias in research, particularly when it comes to implants with inferior outcome than expected. (7) There is limited appetite for a fundamental discussion on these topics in the research societies, even publications of low quality in high level journals were accepted to support the status quo – and the authors refused to comment on letters to the editor and an academic debate (8). It´s hard to justify, that this happened by chance exclusively. The confounders and limitations of basic data decisions are based on has a significant impact on new and innovative devices put on the market. (9)

In addition, we should accept, that some presumptions on clinical research and their use in regulatory processes and administration as well as in individual decisions in patient care are not entirly robust and not supported by empiric observations. This will be explained by three major presumptions, which have proven to be wrong.

1. Clinical Studies can provide sufficient evidence to draw robust important conclusions:

There is evidence, that numbers of subjects included in studies and statistical power are often insufficient. (2-7) The expectation, that published studies are independent and reflect reality in an objective way, is not supported by observation in a retrospective review. (7). For example, outcome and conclusions in publications concerning ASR hip changed significantly after the recall in 2010. The first alarming signals published in the Annual Report by the National Australian Arthroplasty Registry 2007 did not have the same effect. It seems, that publications reflect the common sense in the expert community and rather follow a trend than create a trend. As both regulatory and individual treatment decisions shall be based on evidence it remains unclear how objective conclusions shall be triggered and justified under these circumstances.

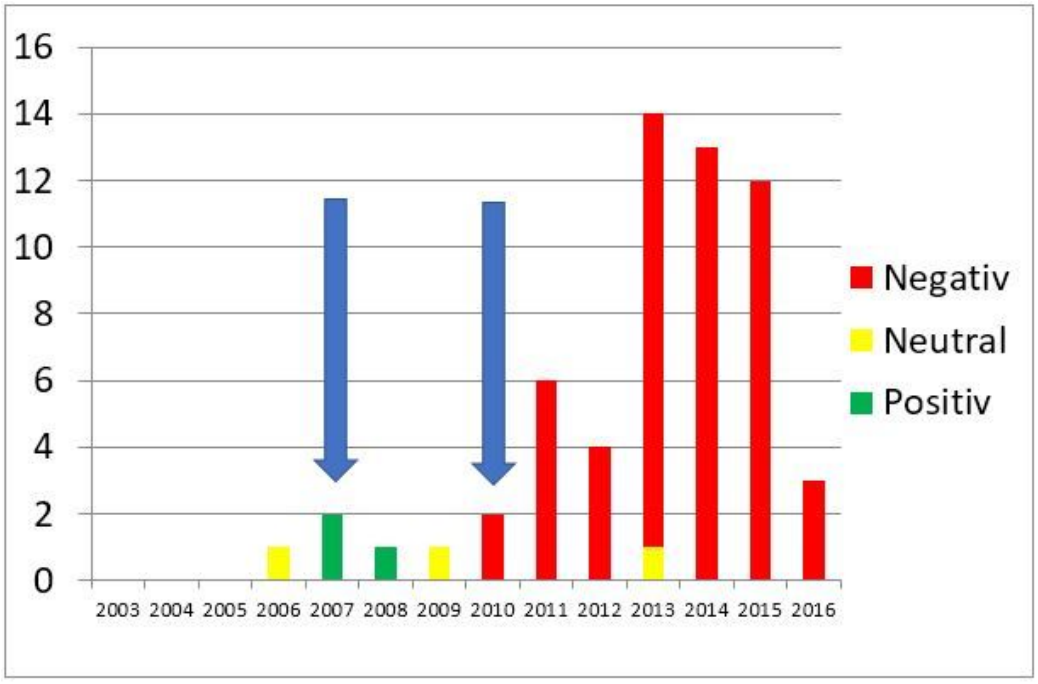

Fig 1: Number and Conclusions in Publications concerning ASR Hip Replacement per year.

2. Clinical Studies can provide robust and meaningful results in reasonable time:

ASR was put on the market in 2003 and within 7 years to recall less than 10 publications with inconclusive results on revision rate for any reason were published. The topic became more attractive after the recall and the related discussion in public and expert fora. Until the recall more than 90.000 patients have received this device. Outcome figures as published in Annual Reports in high level registries like NJR indicate more than 30.000 revisions in addition to what is expected after 7 years to be the result for public health system and patients.

It appears obvious, that publications based on clinical sample-based studies alone are not able to identify even serious incidents like ASR in the time frame expected by authorities and patients in a reliable way. Taking registry data into account at least after 3 years some alarming signals would have been evident.

Uncemented									
Accolade / Trident	26,073	66 (59-73)	44	0.95 (0.84-1.08)	1.91 (1.75-2.09)	2.61 (2.41-2.83)	3.13 (2.89-3.38)	4.46 (4.04-4.92)	*5.24 (4.37-6.28)*
Corail / Duraloc Cementless Cup	4,053	70 (64-75)	39	0.77 (0.54-1.09)	1.71 (1.35-2.16)	2.51 (2.07-3.06)	3.60 (3.05-4.25)	5.58 (4.83-6.43)	*9.69 (8.27-11.35)*
Corail / Pinnacle	137,857	66 (59-73)	45	0.79 (0.75-0.84)	1.60 (1.53-1.67)	2.44 (2.34-2.53)	3.64 (3.50-3.77)	5.96 (5.72-6.22)	
Corail / Trilogy	3,030	68 (61-74)	40	0.65 (0.41-1.01)	1.15 (0.82-1.62)	1.65 (1.23-2.21)	2.23 (1.71-2.90)	3.45 (2.65-4.49)	*4.53 (3.24-6.32)*
Corail / ASR Resurfacing Cup	2,633	61 (54-67)	54	1.07 (0.74-1.54)	7.51 (6.56-8.59)	23.40 (21.81-25.09)	35.48 (33.64-37.38)	43.54 (41.57-45.57)	
Corail / Pinnacle Gription	6,089	67 (58-75)	40	1.00 (0.77-1.30)	1.77 (1.39-2.24)	2.21 (1.68-2.89)	*2.97 (2.08-4.22)*		
Furlong HAC Stem / CSF	17,173	69 (62-76)	40	1.06 (0.92-1.23)	1.76 (1.58-1.98)	2.15 (1.94-2.39)	2.67 (2.43-2.94)	3.60 (3.30-3.94)	5.05 (4.47-5.71)
Furlong HAC Stem / Furlong HAC CSF Plus	22,253	66 (59-73)	45	1.13 (1.00-1.28)	1.84 (1.66-2.03)	2.15 (1.95-2.36)	2.48 (2.26-2.74)	*2.89 (2.31-3.61)*	
Polarstem Cementless / R3 Cementless	8,543	66 (58-73)	46	0.60 (0.45-0.79)	0.93 (0.73-1.19)	0.97 (0.75-1.24)	*0.97 (0.75-1.24)*		
SL-Plus Cementless Stem / EP-Fit Plus	5,402	66 (59-73)	43	1.24 (0.97-1.57)	2.61 (2.21-3.09)	3.78 (3.27-4.35)	4.45 (3.89-5.08)	5.83 (5.14-6.62)	
Synergy Cementless Stem / R3 Cementless	3,348	65 (57-71)	51	0.97 (0.69-1.37)	1.42 (1.05-1.91)	1.95 (1.45-2.64)	3.50 (2.40-5.09)		
Taperloc Cementless Stem / Exceed ABT	22,851	65 (58-72)	44	1.07 (0.94-1.21)	1.52 (1.36-1.70)	1.83 (1.65-2.04)	2.12 (1.90-2.37)	2.16 (1.93-2.42)	

Fig 2: Outcome of ASR compared to similar cups, Source; 15th Annual Report NJR, p 69 Outcome of uncemented THR in Great Britain from 1 to 14 years of follow up. Data on ASR until 10 years, revision rate after 7 years marked.

Resurfacing									
Adept Resurfacing Cup	3,665	54 (48-60)	73	1.15 (0.85-1.56)	2.48 (2.02-3.04)	4.53 (3.89-5.27)	6.24 (5.47-7.10)	8.30 (7.34-9.37)	
ASR Resurfacing Cup	3,071	55 (49-60)	68	1.63 (1.24-2.14)	6.01 (5.22-6.91)	13.67 (12.50-14.94)	20.91 (19.50-22.40)	26.51 (24.96-28.15)	*33.04 (28.72-37.82)*
BHR Resurfacing Cup	21,620	55 (48-60)	74	1.05 (0.92-1.19)	2.36 (2.16-2.57)	3.71 (3.46-3.98)	5.31 (5.00-5.64)	7.95 (7.56-8.37)	11.02 (10.40-11.68)
Cormet 2000 Resurfacing Cup	3,700	55 (48-60)	65	1.52 (1.17-1.96)	3.74 (3.18-4.41)	7.71 (6.89-8.62)	12.15 (11.13-13.25)	17.31 (16.08-18.62)	*23.34 (21.22-25.63)*
Durom Resurfacing Cup	1,728	55 (49-60)	70	1.33 (0.89-2.00)	3.60 (2.81-4.59)	5.53 (4.55-6.72)	7.50 (6.34-8.86)	8.72 (7.45-10.20)	
Recap Magnum	1,755	54 (49-60)	73	1.82 (1.29-2.57)	3.37 (2.62-4.33)	5.56 (4.57-6.75)	7.93 (6.73-9.32)	10.42 (8.94-12.14)	
Conserve Plus Resurfacing Cup	1,350	56 (50-61)	63	2.08 (1.44-2.99)	5.14 (4.08-6.46)	8.23 (6.88-9.84)	10.96 (9.39-12.77)	14.14 (12.29-16.25)	*15.62 (13.30-18.31)*

Note: Blank cells indicate that the number at risk at the time shown has fallen below ten and thus estimates have been omitted as they are highly unreliable.

Fig 3: Outcome of ASR compared to BHR and other resurfacing systems, Source; 15th Annual Report NJR, p 70 Data on Resurfacing THA from 1 to 14 years of follow up.

3. Similarities in implant design and indications lead to similar outcome for the patient:

ASR was put on the market based on claims of equivalence to BHR by Smith & Nephew.

Outcome data show clearly that this presumption is not supported by evidence.

Technical similarities in implant design and similar use do not justify the presumption, that the result of the treatment is basically identical. This is not „only“ relevant for European market approval by equivalence route, but also for 510(k) procedures by FDA in US. The present processes to re-evaluate clinical data and identify such incidents are too long term. MDR will increase monitoring by annual re-evaluation performed by independent experts on an annual base for high risk devices like arthroplasty.

THE NEW MEDICAL DEVICE REGULATION (MDR)

Facing a critical debate on the quality of processes applied to protect the population from serious threat by unsafe implants on 2 incidents, PIP breat implants and ASR hip implants, the EU Commission and EU member states decided to update the legal framework for market access. One aspect on that decision was to upgrade from the current Medical Device Directive (MDD) to the new Medical Device Regulation (MDR). The MDD requested a minimum standard to be implemented in national laws whereas the MDR represents direct applicable law for the entire common market superior to national law. This grants a higher level of harmonisation and better opportunities for fast track interventions, if needed. The decision to a fundamental update of the legal system opened an opportunity to address limitations causing problems by the existing system.

MDR was put in action in 2017 and after a 3-year implementation phase it has to be applied by May 2020. In June 2016 by publication of guidance document MEDDEV 2.7/1 rev 4 the key points concerning clinical data were included in present requirements. (10) As a guidance document is expected to be followed the main impact on clinical data is already applicable, even MDR is still in transition phase.

The new legal requirements did not “only“ refer to identified topics for improvement. As the real world changed in the past decades dramatically by introduction of IT and comprehensive documentation in medical care it is one goal to include new opportunities and reality of the present world, we life in into legal requirements. The devolpment of registries in the past decades and their positive effects are a perfect example on the benefits by this megatrend for healthcare and patients. (11)

NEW REQUIREMENTS OF MDR

In terms of clinical data there are 2 important new requirements (1, 10).

1. Systematic Reviews have to be considered. This includes all kinds of evaluation on evidence relevant for a device like Cochrane Reviews, published Metaanalyses or Health Technology Reports. In addition, guidelines or statements by experts’ societies are to be considered if they refer to state of the art.

2. Registries as new source of clinical data are to be considered.

The definition of “Register“ in regulatory settings is different and wider than the one generally used in orthopaedic research. The definition of AHRQ (Agency for Healthcare Rssearch and Quality) as accepted by global regulatory bodies by IMDRF (International Medical Device Regulatory Forum) is:

“An organized system that uses observational study methods to collect uniform data (clinical or other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s)”

This definition does not “only“ include well known national quality registries like in Sweden, Norway, the NJR in UK, RNE in Romania, SAR in Slovakia or EPRD in Germany. It includes also all kind of quality registries on local or institutional level, registries run by manufacturers, routine data collected by hospitals, sick funds or other public health institutions, data generated by active medical devices or apps, all aspects of telemedicine as well as cohort studies like Framingham Heart Study. In fact this definition covers „Real World Evidence“ in it´s wider scope.

Manufacturers have to collect and evaluate registry data in a robust standard procedure. This leads in a general view to implementation of "Industry 4.0" in medical device industry and will affect almost all parts of a company. As manufacturers have to get access to at least a representative sample of the market for a specific device they will have to organise that on contract base and establish regular and ongoing cooperation with registries, which act as data suppliers to their quality management system. Certainly, there will be a higher demand on expertise on the registry data and clinical data analyses in general at all stakeholders. The assessment inside the company has to include all relevant aspects of safety and performance. If, for example, a manufacturer identifies signals, that indication is “overstreached“ for a certain device, it has to react by information of all surgeons and users of their devices. In case of identified implant with inferior outcome the manufacturer must not leave surgeons alone to deal with individual patients. They have to provide information and proposals as well as rational and supporting evidence to the users of their devices.

BETTER INTERACTION BETWEEN MANUFACTURER AND CUSTOMERS

Another result – hopefully – will be a more transparent interaction between manufacturer and physicians using their devices. In the past information to physicians was often „filtered“ in case of incidents or critical discussion. There is at least the legal obligation for manufacturers to provide objective evaluation of all clinical data available (i.e. studies, registries, complaint reports,...) in a Clinical Evaluation Report. For high risk devices like arthroplasty a summary report has to be published by a website of the EU called EUDAMED after assessment by the Notified Body. When necessary certainly physicians can request access to the Clinical Evaluation Report to draw the own conclusion on the evidence avialable.

As this is a legal document, comprehensive and objective information on all available clinical content has to be included and subject of appraisal. To provide access to external experts might create controversial discussions with customers of the company. So, one should not be surprised if manufacturers might be reluctant to provide this document. But even if access is denied, in conjunction with the quality of other information provided, it might be a signal to users of a device how transparent manufacturers deal with the subject in support of their customers for their service to patients. On that end support and cooperation by users of the devices, for example by taking the legal obligation to report potential implant deficiencies to manufacturers and authorities serious, is essential to assure proper function of regulatory procedures in support of safe and effective devices to be used for treatment.

DEVICE DEVELOPMENT WILL CHANGE

By introduction of more stringent quality management systems at manufacturers the way how new devices will be developed will change. The genius idea of an implant designer will be replaced to some extent by a more robust and careful process including many „check and doublecheck“ steps according to a defined plan. This might include more lab-testing on relevant topics for safety and performance. Copy-paste of smart ideas by other devices will be more difficult as they have to be subject of inhouse testing, even if they seem to be well established. In summary device development will become more expensive by increasing testing and validation procedures of parts of the device and the entire system. Product development from a surgeon’s point of view will become more teamwork than single expert projects. Consequently, the „trial and error“ approach, which was used in many

cases in the past will be constrained by regulatory interventions. Manufacturers will be more critical when it comes to challange business plans prior to start development projects. It appears likely, that development of new drugs by start up companies – which are sold to large companies to perform the final steps to market approval and marketing – might be a proper example for medical device development in the future.

SCIENTIFIC LANDSCAPE WILL CHANGE

By introduction of registries and new source of clinical data the future landscape of scientific projects is likely to shift. Randomised controled trials are the gold standard when it comes to internal validity (i.e. to control bias by conducting the study like patient selection or documentation). ISO 14155 is the relevant standard for medical devices, and it is basically very similar to Good Clinical Practice and standards for conducting pharma-studies. Certainly, this will provide significant added value when it comes to innovative technologies or devices and to provide causality for specific questions. But most important for medical device outcome is external validity (i.e. the data reflect the reality of average patient care avoiding confounders by special local procedures or expert centers) as the way to use devices has a significant impact on the over all outcome. For MDD, when sample based clinical studies were the main source of clinical studies follow up studies were the best option available. Despite well known limitations like insufficient statistical power by insufficient number of patients or the fact that the majority of studies are conducted in special centers like university hospitals these studies represented the major data sampling in the past.

With introduction of registries as potential source of clinical data this changes dramatically as by the new requirements routine documentation can be used to provide evidence to confirm safety and performance. This refers to national and other quality registries, routine documentation in hospitals and public health systems as well as data collected by devices during operation. They can provide more accurate and reliable evidence on a device for much lower costs as the most expensive part of studies is data collection. These costs are almost neglectable when data are already available in a structured way and just have to be downloaded by a filter. As a result, regular follow up studies will become less attractive for manufacturers to be supported. On the other hand, to provide evaluated routine data might create an additional and new opportunity to receive support for research teams at hospitals. However, the landscape will change as manufacturers will have to provide a representative sample of the market to regulators, so they will have to include all types of hospitals rather than focus on „expert centers“. Hospitals providing data will have to run a professional support system for this service. But the money for groups of study nurses and other resources to run a study in the past will shift more to data extraction and professional evaluation needs. This will create a change situation for financial support to research groups with all opportunities are risks of such disruptive changes.

CAUSALITY VS CORRELATION

When it comes to evaluations it is important to consider, that sample based clinical studies and registries have different focus on organisation, evaluation and validity of results.

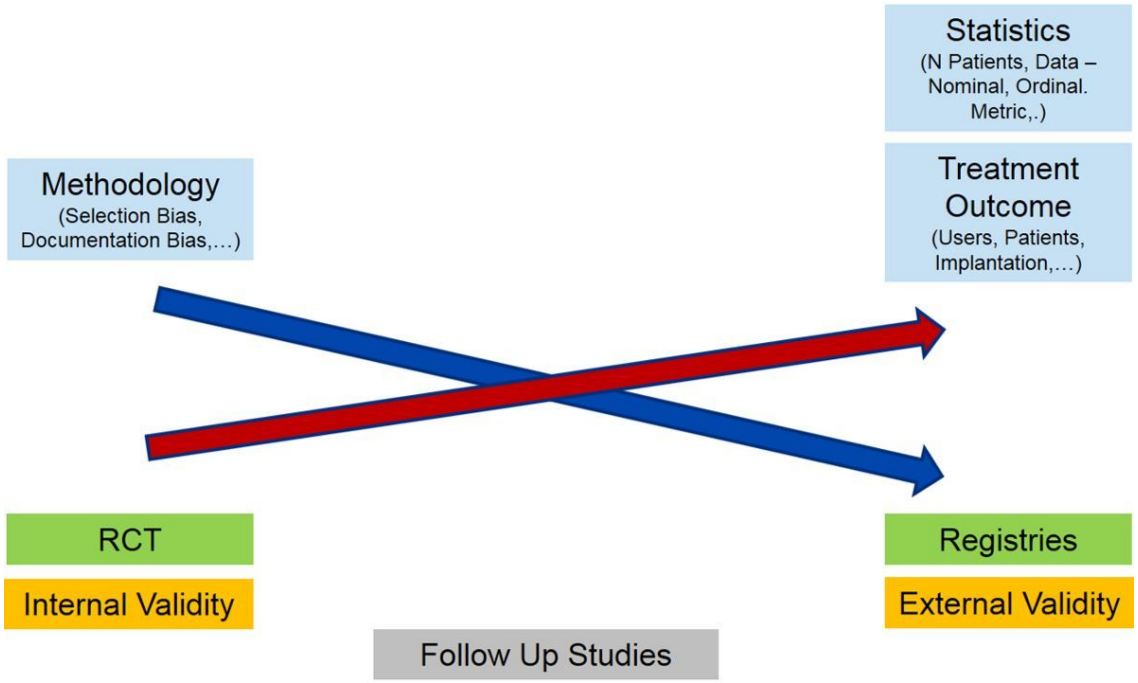

Fig 4: Focus for high quality Studies and Registries for Evaluations.

Randomized Controlled Trails have an advantage when it comes to create evidence on a specific question in a well controlled environment. To confirm causalilty on a specific question for example. This is important in innovative topics, during early stages of device development or to drill down in newly identified topics. Registries have an advantage when it comes to confirm presumptions, for example whether expectations on the outcome of a device are true in average patient service. Follow up studies combine the limitations of both ends of the spectrum on validity and are less attractive for the circumstances of future regulatory requirements. RCT´s and other confirmatory study designs aim to provide causality supported by statistical evaluations. Registry evaluations provide information or correllations, which might lead to misinterpretation when statements on causality are done. A well knwon example is the correlation of decreasing birthrate and storch population.

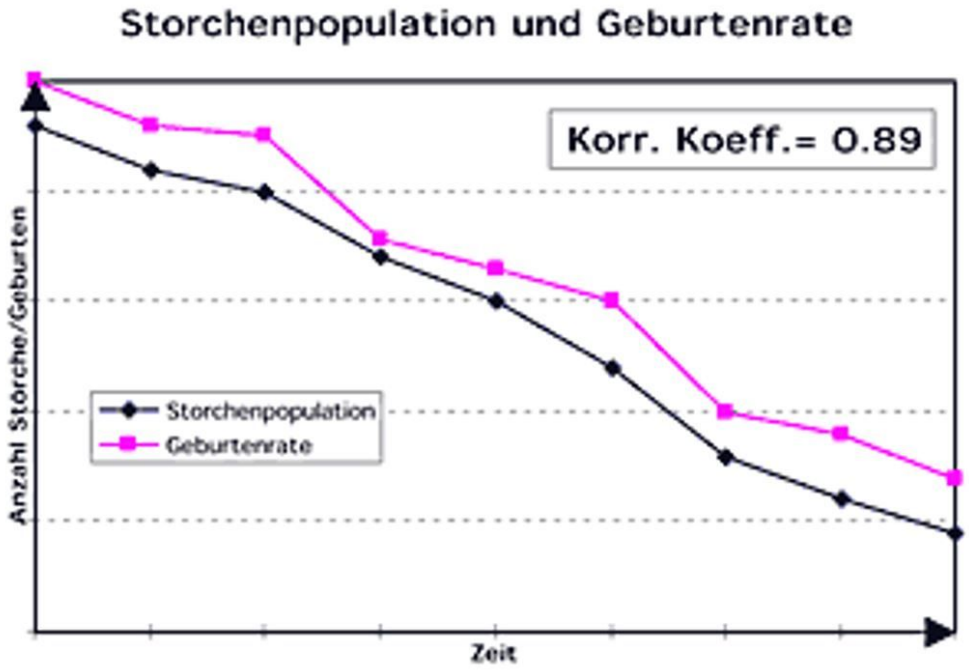

Fig 5: Storch population and birth rate over time Source: https://basler -regionalnetz.ch/uploads/pdf/Einf%C3%BChrung%20Statistik%20wiesbeck%202017.pdf

One could conclude, that this provides evidence that the storch delivers babies. To avoid such incidents a higher level of specific clinical and methodological expertise is required as causality is required to confirm regulatory requirements. When using real world evidence data statistical procedures are different from the ones used for sample-based studies. (Lit 14-17). Big Data analyses are basically no new subject. It has to be included in evaluations of clinical data, too. This means, that it is not possible to run the same procedures for any source of clinical data and adaption to that is necessary.

THE ROLE OF HOSPITALS AND RESEARCHERS

New regulations will require more quality and quantity of clinical data and evidence. From methodological point of view it will become more complex to perform a proper evaluation as there are different requirements for individual sources of data. To judge whether data from a study or a registry are superior in case of inconsistent outcome will be challenging.

As manufacturers are by law responsible to provide evidence on their devices they have some interest to support studies on their devices. In the past these were in majority sample based follow up studies as they met the requirements by regulation. In the future a shift to registry data is to be expected and this will have an impact on funding opportunities. The quality and quantity of clinical data and evidence to put devces on the market and to maintain market approval will increase. For any expert or hospital interested to participate and benefit from financial support it will be important to respect the basic principles to support a regulatory system. This includes for example to provide transparency and stick to general rules on research and cooperation with other stakeholders in the regulatory system. This refers for example to reproducability of results, the possibility to monitor and verify clinical data, which were used for decisions, or to accept legal standards which are maybe not relevant for patient care and research activities on he same level at the moment. To safe data and other relevant source of information like retrievals, report potential failures proactively and to keep data protection for patients are just some examples.

From a researcher´s perspective conflicts of interest might be relevant, too. For example, when alarming signals are detected this is often interesting content for publication. On the other hand, regulatory bodies are most probably not happy to wait until publication to move forward with their actions. As regulatory processes are subject of confidentiality it is possible to handle that by agreement – if this is addressed in advance. The same principles relevant for financial support are also important for carreers of researchers. The impact by regulation on research will grow by the increasing importance of clinical evidence. This will lead to some split of research. Certainly, any type of academinc research is and will be free. But when it will come to research to support regulatory processes – and this is the majority of research supported by industry grants – expectations by regulatory should be taken into account. In fact, this leads to some regulation of research Basic expectations beyond research and publication standards should be taken into account.

Higher demands on evidence will create opportunities for researchers in a wide scope. But the higher demands on quality of research output will also request a higher level of professional execution of studies and evaluations. There are guidelines and standards by regulators to be respected and manufacturers will have to obey these rules. As recent analyses of state of the art to any device will be required and publications on that are applicable to regulatory processes it will become more attractive for journals to publish such articles. A good chance for junior researchers to start a carreer and get familiar with evidence on the implants and treatment they perform.

CONCLUSION

The new regulatory framework of MDR will have a major impact on research. As results by clinical research is subject of increasing recognition the requirements on researchers and research projects will increase. One of the main aims of the new regulation is to utilize real world evidence to monitor and assure safety and performance of medical devices. Arthroplasty with it´s history and quality registries of almost 50 years is a pioneer on that subject. However, the definition of registries is not limited to quality registries as we are used to. It includes a wide range of clinical data, which allows in fact every physician to participate, support actions to increase safety and performance for patients and to benefit from new opportunities. We are ahead of a disruptive change situation and a window of opportunity to develop for the next level of patient safety.

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