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Clinical Evidence stimulates Innovation:

An asset for surgeons, an ally for patients

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Curiosity is a major driver for innovation, with the aim to improve patient care. Total hip replacement was called the operation of the century (i.e. 20th century) (1). Some state no real innovation has happened in Orthopaedics since then, they blame increased bureaucracy, while others are still curious on how to improve patient outcome. Considering arthroplasty surgery, two of the major problems are aseptic loosening of an implant and prosthetic joint infection (PJI). Both having an enormous impact on patient's quality of life and can be life threatening if performed inadequately. Innovations in arthroplasty surgery are generally technique oriented, from implementing computer assisted surgery, to percutaneous refixation of loosened implants with gene therapy (2), to induction heating of infected implants (3). More recent, innovation focusses on big data for better outcome, thus benchmarking hospital performance (4). The latter, healthcare evaluation research is "low- hanging-fruit" research (e.g. Why am I giving 2 days of antibiotics etc) which is relatively inexpensive, but will have a huge effect on clinical practice. Even more such research can be easily implemented with regional or national groups of surgeons. In essence it goes back to, no innovation without evaluation (IDEAL consortium). The latter stresses the aim of *real* innovation: improving patient care, which goes hand-in-hand with patient safety. Although this is always the intention, innovations may have an opposite, harmful effect to patients.

Active and ageing populations are expected to have a tremendous impact on the number of hip and knee arthroplasties to be performed in near future. These populations might experience an orthopaedic problem somewhere in future. As for joint replacing implants, like hip, knee, shoulder, about 4 million are performed on an annual basis. Which medical device to use for which patient and for that matter which medical device is asked for in some countries is based on personal preferences of surgeons and the availability of orthopaedic vendors. Evidence based clinical practice seems to be hyped terminology which is around for decades, but in the end value added healthcare to the patient, or an implant lasting a life time, should be the goal of an orthopaedic surgical intervention. Evidence should not be based only on a single center study if real world data from (complete) regional or national arthroplasty registers are available. For the surgeon, these registry data can identify best performing from mediocre performing implants. But these data should be interpreted with care by orthopaedic surgeons who have knowledge on methodology of data analysis (e.g. confounders, bias, risk adjustment, case mix corrections).

Although data from joint implant registries are only available from some large registries like the NJR (UK, Wales, North Ireland, Isle of Man) , AOANJRR (Australia), LROI (Netherlands), NARA (Scandinavian countries), to mention the largest four, several smaller regional registries are present in Europe (12). Germany has started in recent years and has already a coverage of 70%, the US registry is small and has a capture rate of 29%. The value of implant registries was shown by detecting the high revision rate of the metal-on-metal (MoM) hip articulation problem, detected in 2010, the best-known worldwide disaster in Orthopaedics. It was detected from a single national registry —

Australian Orthopaedic Association National Joint Replacement Registry. Soon thereafter it was picked up by several other national registries worldwide, showing similar outcomes with this type of hip replacement. This information ultimately resulted in the withdrawal from the market of certain MoM total hip implants. But only after hundred of thousands of patients had these implants during several years. An evidence-based approach for the introduction of new implants as proposed for decades by several authors (8, 10, 12, 13) and a classification on the performance of implants would have prevented such a disaster, if surgeons adhere to principles of evidence based clinical practice (5). As for a benchmark for implants, the Orthopaedic Data Evaluation Panel (ODEP) is worldwide widely used. Such a benchmarking system helps guide, not dictate, a surgeons' choice for an implant with the most optimal outcome for their patients. Preferably, implants with the highest benchmark classification (i.e. 95% survival at 10 years) should be based on data from at least two national registry. Thus, registers can be used to guide orthopaedic surgeons in their choice of an implant for a specific patient based on real-world data from a high validity registry (9, 17). The latter implies > 95% coverage and > 95% completeness of all implant surgeries done.

In May 2021 (with a transition phase of some years), the EU will implement the new medical device regulations (MDR) on medical implants, in vitro diagnostics with the aim to safeguard patient safety by showing clinical evidence (7). The former lack of adequate regulation by both the former EU Directive and FDA regulation is repaired for the better of patient safety (and efficacy of the medical device). In the past this lack of evidence has led to the widespread use of potentially unsafe TKA and THA (e.g. metal on metal hip), with failure rates two to ten times the standard of national joint registries (9, 13). Taking the above into consideration, the selection of any new implant including new surgical techniques should be clinically evaluated and clinically proof their claims. The lattes is in accordance with the IDEAL consortium adagium: *no surgical innovation without evaluation*. The following stages for a safe and effective introduction of a new implant or surgical technique are: Idea, Development, Exploration, Long-term study (IDEAL (5, 17)).

A phased, evidence-based introduction of orthopaedic implants has been advocated for several decades now (8, 10, 12, 13) and has indeed been picked-up, but slowly. The huge Asian market will profit from lower revision rates (i.e. 10% revision at 5 years or 5% at 5 years) will have a huge impact on not only patient's quality of life, but also on societal economic burden. This phased introduction of new implants is pushed by some major adverse events, like the metal on metal hip implants. The latter had high revision rates, and long-term adverse events (15). A phased evidence-based introduction of new implants can identify three modes of implant failure:

I. Expected, early detected failures
II. Expected, late detected failures
III. Unexpected failures

Expected, early detected failure modes are discovered in a pre-market setting (e.g. fatigue of metal, liner wear). Expected, late detected failures are discovered in a post-market setting (e.g. excessive early migration of the implant). Unexpected failure modes can be present in both the early pre-market and late post-market phase, depending on the type of failure mode (e.g. excessive migration of the implant, biological response like pseudotumors of metal on metal implants) and material breakdown (e.g. modular femoral neck fractures). In general, the longer the pre-market phase will last, the higher the likelihood of finding unexpected failures. Although evident failure modes will be detected in large patient groups after several years of implantation, the goal of a new implant should be to prevent adverse events before mass introduction in the market! Such an early detection modality of both early, late and unexpected failures can be done by evaluating real world data of daily practice from high quality regional or national implant registries. These registries should have a completeness of both primary as well as revision surgery of at least 90 and preferably over 95% to prevent selection bias (17). Even more, presence of unexpected failures, which are usually rare (e.g. periprosthetic

fractures), stress not only the importance of high completeness of these data, but also the importance of collaboration between these national registries as is advocated by NARA (Nordic Arthroplasty Registers), NORE (Network Orthopaedic Registries of Europe, an EFORT committee (11)) and ISAR (International Society Arthroplasty Registries).

Despite the value of registries in a phased evidence-based introduction of new implants, detection of failures will usually be present at mid-term or even later follow-up after exposure to tens of thousands of patients. An early detection of a possible long-term implant failure would not only protect thousands of patients from high loosening rates at 10 years, but would also help the industry in designing earlier better implants (i.e. with less micromotion in the bone). Such surrogate markers during the first postoperative year which are predictive for long-term implant survival at 10 years are implant micromotion measurements in 3D, like RSA (12, 14, 18, 19, 20). This implant micromotion technique can bridge the gap between an evidence-based introduction of new implants and early high quality outcome. Furthermore, since measurements are accurate in up to 0.1mm and 0.1 dgr only 50-60 patients are exposed to a new implant in a high quality study comparing the new implant with the old implant. These implant micromotion measurements, like RSA are validated surrogate markers for long-term THA and TKA outcome (12, 14, 18, 19, 20). The effect on society if RSA-tested TKA are used, gives an estimated 22% to 35% reduction in revision for any reason compared to non-RSA-tested TKA in several national joint registries (12).

Unexpected failures also require vigilance from surgeons not only interpreting data from national joint registries, micromotion studies, but also discussing and evaluating instrumentation, surgical techniques, adverse events of the first cases with surgical users. For that matter, proof of superior effectiveness has become more challenging nowadays than in the past, but more surgeons start to adopt a more scientific strategy - based on clinical evidence- when selecting an implant. This imposes pressure on these first user surgeons to evaluate and analyse their results of the surgical intervention and patient outcome of the new product in a rigorous way. Such a system of surgeon user panel evaluation (i.e. Beyond Compliance), where surgeons discuss with surgeons their data and their experience with the new implant and instrumentation, improves outcome for patients but also product innovation.

A phased evidence-based introduction of new implants that examines every possible mode of expected and unexpected failure will be a challenge. A TOI, Toolbox Orthopaedic Implants, could be used both for existing and new implants:

- existing implants: an excellent implant has a mean 95% survival at 10 years based on data from at least 2 registries
- new implants: implant micromotion studies, Beyond Compliance, patient (reported) outcome measures.

A curious, but critical appraisal of clinical evidence is a must, not only for patient safety, but also to develop innovative medical devices which show real improvements (1,6,16). This seems logical, since physicians intend to improve patient's quality of life for thousands of years, but sometimes the *primum non nocere* turns into a nocebo effect,

which should be minimised for an optimal patient outcome. Innovation and evidence are not conflicting objectives, but no innovation without clinical evidence, this safeguards optimal outcome for patients.

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