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# Introduction of innovations in joint arthroplasty: Recommendations from the 'EFORT implant and patient safety initiative'

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- With the implementation of the new MDR 2017/745 by the European Parliament, more robust clinical and pre-clinical data will be required due to a more stringent approval process.
- The EFORT Implant and Patient Safety Initiative WG1 'Introduction of Innovation', combined knowledge of orthopaedic surgeons, research institutes, orthopaedic device manufacturers, patient representatives and regulatory authorities to develop a comprehensive set of recommendations for the introduction of innovations in joint arthroplasty within the boundaries of MDR 2017/745.
- Recommendations have been developed to address key questions about pre-clinical and clinical requirements for the introduction of new implants and implant-related instrumentation with the participation of a steering group, invited by the EFORT Board in dialogue with representatives from European National Societies and Speciality Societies.
- Different degrees of novelty and innovation were described and agreed on in relation to when surgeons can start, using implants and implant-related instrumentation routinely.
- Before any clinical phase of a new implant, following the pre-market clinical investigation or the equivalent device PMCF pathway, it is a common understanding that all appropriate

**Keywords**

- EFORT implant & patient safety initiative
- recommendations IPSI WG1 introduction of innovation
- new implants and implant-related instrumentation
- joint arthroplasty
- medical device regulation MDR 2017/745

pre-clinical testing (regulatory mandatory and evident state of the art) – which has to be considered for a specific device – has been successfully completed.
- Once manufacturers receive the CE mark for a medical device, it can be used in patients routinely when a clinical investigation has been conducted to demonstrate the conformity of devices according to MDR Article 62 or full equivalence for the technical, biological and clinical characteristics has been demonstrated (MDR, Annex XIV, Part A, 3.) and a PMCF study has been initiated.

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## Introduction

The patient, surgeons, industry and health care system need efficient and safe implants. To increase safety but still have new implants, the 'EFORT Patient and Implant Safety Initiative (IPSI)' was launched in January 2020 by the European Federation of National Associations of Orthopaedics and Traumatology together with a 1st EFORT European consensus initiative on 'Introduction of Innovations' (1). Due to the ubiquitous and increasing need for arthroplasty surgery first, the scope and activities of IPSI WG1 and the 1st EFORT European Consensus concentrated on the topics of new implants and implant-related instrumentation in this area.

Orthopaedic surgeons, scientists, representatives of health policy, regulators, implant manufacturers and patient organisations participated in a working group, which discussed the following questions:

- What are the expectations of stakeholders (patients, surgeons, industry, authorities, society) for a new implant and implant-related instrumentation?
- How is innovation in the area of implants or implant-related instrumentations defined?
- What are the pre-clinical requirements for the introduction of new implants and implant-related instrumentation?
- What are the clinical requirements for the introduction of new implants and implant-related instrumentation?
- When can surgeons start, using an implant and implant-related instrumentation routinely?

There is also a need for innovation like artificial intelligence, computer-assisted surgical procedures, three-dimensional-printed implants and instruments, new biomaterials and smart implants are currently being developed. This need is justified by a wish for improvement in patient treatment. A recent example was the large-diameter head metal-on-metal hip arthroplasty technology based on the hope of a better outcome. This turned out to be a catastrophe for many patients and is an example of enthusiastic dissemination of available new products with insufficient clinical and pre-clinical evaluation of the innovation in terms of insufficient validation of clinical outcomes and side effects. This stresses that the new Medical Device Regulation (MDR) is warranted.

Introduction of new treatment techniques, modified strategies or innovative implants must strictly follow rules of proper evaluation, regulation and training in order not to put patients at unnecessary risk (2, 3, 4). Although different recommendations regarding 'phased' or 'stepwise' introduction of new treatment techniques into clinical practice have been proposed early (5, 6, 7, 8, 9). But, the development, implementation and dissemination of surgical innovation have not always been properly conducted in recent years, resulting in less optimal outcomes for patients (10).

With the implementation of the new MDR by the European Parliament, several already existing rules for the introduction of innovative products and instruments have been tightened, and even new rules have been established. More robust clinical and pre-clinical data will be required due to a more stringent approval process for medical devices.

The regulatory framework is extensive, but there is a lack of understanding and clarity in daily practice what the meaning of clinical and pre-clinical evidence as required by the MDR. It is often unclear for orthopaedic surgeons, what a 'surgical innovation' is and when an implant is sufficiently validated for market access (i.e. CE certification) and routine clinical use. These questions are of utmost importance for the introduction of new implants and implant-related instrumentation and for a comprehensive understanding of all factors influencing the risk of complication. Thus, there is a need for clarification to ensure the safe treatment of patients and the use of implants.

A phased introduction of new implants appropriately considering the state-of-the-art pre-clinical and clinical methodologies can identify failures (Table 1).

An appropriate follow-up is needed for the detection of different types of complications both early and late. Although evident failure modes will be detected in large patient groups after several years of implantation, the goal of a stepwise introduction of a new implant should be to prevent adverse events before broad introduction in the market. Such an early detection modality of

**Table 1** Early, late and unexpected detected failures.

| Detected failure modes | Typical scenarios (exemplary) |
|---|---|
| Early failure modes in pre-market setting | Fatigue failure of implants |
| | Liner wear |
| Late failures in the post-market setting | Excessive early migration of the implant |
| | High rate of early aseptic loosening |
| Unexpected failure modes – early pre-market and late post-market phase | Biological response like pseudo-tumours formation related to metal-on-metal articulations |
| | Implant material corrosion |
| | Modular femoral neck fractures |

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. Unexpected failures also require vigilance from surgeons not only interpreting data from national joint registries, and that is, radiostereometric-analysis (RSA) or computed tomography (CT)-based micro-motion studies, but also discussing and evaluating instrumentation, surgical techniques and adverse events of the first cases with surgical users. Such a system of surgeon user panel evaluation, where surgeons discuss with surgeons, experts and researchers their data and their experience with the new implant and instrumentation, improves outcome for patients but also product and surgical treatment innovation. There is a need for controlled introduction of a new implant and data sharing between countries to learn from early complications.

## Expectations for the new implant and implant-related instrumentation

### *The medical need*

A clear medical need with an appropriate risk–benefit ratio should be addressed by the innovation (implants and implant-related instrumentation, new treatment techniques, modified strategies, etc.) that stands for certification

### *The patient expectations*

Less pain, better mobility, longevity of implant (maintenance), Quality of Life improvement, less medicaments, better sleep, fulfilment of (individual) expectations, return to work, sports and activities of daily living, rapid recovery, a safe implant with reduced risk of complications and good information pre-op.

### *The surgeons expectations*

Meets unmet needs, good pre-clinical documentation (including design and material characterisation, biomechanical and biotribological testing as well as human donor and animal studies if applicable, bone and ligament sparing implants, less risk of infection, good and reproducible clinical results, pre-operative planning and intra-operative documentation, satisfied patients, forgiving implants and related instruments tolerant to deviations (i.e. bone preparation, implantation, etc.) within a certain range, easy and safe application (resilient device, reproducible instrumentation) vs more complex device, saving surgery time, reduced surgical trauma, allows for stringent surgical workflows, economical sustainability, forgivable during implantation; can components be revised after 10 or more years?; is it revisable without creating large bone defects and complications? intra-operative flexibility to react on unexpected situations (i.e. for knee ligamentous deficiency or instability, by providing knee implant options with a higher degree of tibio–femoral constraint within an implant and instrument platform), modularity for revision options and treatment of severe bone defects, should be open to have surgical skills training class for new surgeons using it; Adhere to principles of good clinical practice and stimulate data collection within registries.

### *The industry*

Safe implant and implant-related instrumentation, closing both gaps of surgeon needs and patient's needs, is it forgiving and revisable at long-term?, meet market or surgical school driven specific needs (worldwide), process and manufacturing related benefits (cost), economical and ecological sustainability, unique selling points (differentiation), foreseeable regulatory processes and timelines, smart customer-oriented processes and logistics (consignments, loaner pools, etc.), smart knowledge transfer to surgeons and hospitals (i.e. recommendation to surgeons to take a -short- hands-on training or surgery with a trained colleague, when using a new implant), interaction to adjacent research fields (i.e. infection prevention or active treatment), combining up-coming technologies with implants and implant-related instrumentation (i.e. digital transformation, navigation, robotics, artificial intelligence, etc.) for further optimisations in close collaboration with academic research.

### *Academia*

Define in close collaboration with clinicians, clinical scientists and experts from industry minimum requirements for pre-clinical and clinical evidence.

### *Authorities and society*

Innovations in areas with public health problems/ unsolved needs are of high priority. The new implant

must demonstrate safety and performance, that is, DMC regarding health economic considerations.

## How to define the new implant or the implant-related instrumentation

*Does any modification of an existing implant or implant-related instrumentation represent a 'new' implant/instrument and how could different types of modifications be distinguished?*

To determine the methods required to assess implants/instruments prior to approval by the notified bodies, it is necessary to consider the novelty of the specific implant/instrument, that is, the types of modifications made in comparison to the predecessor product. Not all modifications of existing implants/instruments may lead to a 'new' implant/instrument, but this strongly depends on the nature of the modification. It has to be acknowledged, that it is quite difficult for the medical device companies, notified bodies, expert panels and surgeons to know in advance what changes would have no effect on the implant performance (11, 12). Therefore, any modification shall be evaluated and documented following a risk-based approach in line with the actual version of the standard ISO 14971. Validation of the clinical effect of any modification is mandatory, but the definition of the appropriate methodology (i.e. adaptation of risk analysis, additional pre-clinical testing, clinical evaluation, clinical study) depends on the specific case (see following descriptive examples).

Different types of modifications could be distinguished based on the respective levels of innovation (from low to high):

(a) Design modifications which might not have any direct influence on implant performance/fixation/patient, that is, minor optimisations on given implants.

Some examples are an adjusted radius in the locking mechanism between the acetabular cup and insert; a different shape of radiologic markers in polyethylene acetabular cups; design changes in the instrument–implant interface such as the change from hexagon to torx socket; a change in the curvature of a hip stem's distal tip for easier implantation, but without influence on implant stability based on adequate pre-clinical testing.

(b) Additions to already existing sets of implants.

Some examples are the same implant in additional sizes. Thereby, it is important to assess if this addition represents a new worst case. Smaller or larger sizes are definitely likely to generate more critical scenarios (i.e. a cemented titanium stem whose sizes influenced the clinical result or a hip stem with excellent Swedish registry results, but inferior behaviour of a small size), and should therefore be considered as 'risky', whereas intermediate sizes are less likely to create a new worst case.

(c) Design changes with direct influence on implant performance/fixation/patient.

Some examples are new radii or trochlea groove in a femoral knee component, changes in the distribution of coatings for implant fixation, a modified instrumentation or surgical technique (i.e. different bone preparation) or an extension of the usage to a different patient group (i.e. Asian population, different anatomies, severe deformities, dysplasia, etc.).

(d) New material, that is, a material which is new in this explicit application, but already known from other orthopaedic applications or an essentially different manufacturing process for the same material as used before, as well as new or modified surface treatments (i.e. polishing, shot-peening, grit-blasting, porous coating, hydroxyapatite coating, etc.).

Some examples are Vitamin E-stabilized polyethylene in total knee arthroplasty (TKA), which has already been applied in total hip arthroplasty (THA), but moderately cross-linked, slight PE processing changes (i.e. Mrad dose for sterilisation, etc.) or a completely different manufacturing process (i.e. using additive manufacturing of titanium alloy instead of forging or casting, etc.). It is obvious that not every material change will require a new study, but a risk-based approach shall be followed towards identifying the impact of this change on the clinical safety and performance of a device.

(e) Innovation, that is, a completely new implant design, feature or material.

Some examples are an anti-microbial coating on implants; pressure sensors in implants to record overload; a knee implant completely made of alternative materials like poly-aryl-ether-ketone.

(f) Design changes with direct influence on implant performance/fixation/patient combined with a new material (c + d) or design changes with direct influence combined with an innovation (c + e) or a new material combined with an innovation (d + e) or a combination of all three (c + d + e).

Some examples are a modified implant combined with a new surgical technique (c+e) or are new cup design based on additive manufacturing with a new lattice structure at the implant–bone interface (c+d+ e).

*How could a true novel implant be distinguished from an implant where equivalence is claimed?*

Regarding equivalence, technical, biological and clinical characteristics are relevant and should be based on a

risk analysis with an objective evaluation of the potential failure scenarios. An equivalent material or implant must show at least similar critical test performance results as the reference material or prostheses.

Technical*:* The device must be of similar design including conditions of use and principles of operation, have similar specifications and properties, that is, surface characteristics and have similar critical performance requirements.

Biological*:* The device must use the same materials or substances with similar release characteristics in contact with the same tissues also regarding kind and duration of contact.

Clinical*:* The device must be used for the same clinical condition and purpose, considering also severity of disease, population characteristics (i.e. age, anatomy, physiology) and site in the body, it has the same users and similar relevant critical performance characteristics for a specific intended purpose. Furthermore, the claimed clinical advantages should be shown during clinical evaluation (i.e. better bone fixation by RSA, or new methods like observer-independent x-ray analysis for *in vivo* wear measurements, migration and osteolysis, better flexion by improved range of motion).

According to those preconditions, the types of modifications (a) to (c), that is, (a) design modifications which have no direct influence on implant performance/fixation/patient, (b) additions to already existing sets of implants and (c) design changes with direct influence on implant performance/fixation/patient could be regarded a 'novel implant with equivalence' when a clear demonstration and justification of equivalence is present. It has been established that the extent of equivalence is such as there exists no clinically significant difference affecting the safety and performance of the device. In addition to that, it is especially important for type (c) that a modification must have a benefit for the patient. It remains clear that any implantable device, which will be distributed on the EU market based on the equivalence route would need to confirm safety and performance in a Post-Market Clinical Follow-up (PMCF) study after CE-marking.

The type of modification (d), that is, new material, certainly marks a transition from 'novel implant with equivalence' to 'true novel implant', that is, a demonstration of equivalence can still apply and be successful for specific characteristics, but surely clinically relevant aspects remain which cannot be addressed relying on equivalence alone. However, even for type (e), that is, innovation, this might still be an option. There are some examples where a change in material might be acceptable when the change in the material composition might lead to increased patient safety due to removal of carcinogenic, mutagenic or reproductive toxicity substances (i.e. removing of phthalates) or leads to optimisations and improvements aspects based on other criteria, which can be supported either by clinical or other evidence. It is obvious that the system would still need to take into consideration that this would only improve the risk to the patient regarding that specific factor and that the device would still need monitoring in case the change gave rise to an increase in some other risk factor or failure mode.

Ultimately, there are types of modification (e) and (f), thet is, (e) innovations and (f) combinations of design changes with direct influence on implant performance/fixation/patient, new materials and innovations. They represent either a device containing a modification which must be considered a true innovation for which no clinical data currently exists, and which has a relevant impact on the safety and performance or a combination of modifications, that is, a relevant design change combined with a new material.

Such a device must certainly be categorised as 'true novel implant' as there are relevant aspects which can individually or in combination not be addressed by considerations based on equivalence alone.

### *How can a new/different 'claim' be supported by scientific evidence?*

For the support of a new or different 'claim', no direct link to the aforementioned levels of innovation can be established as it always depends on the specific claim of clinical superiority to the old design. In general, scientific evidence is required for any claim, which can be proven during pre-clinical (design and material characterisation, biomechanical and biotribological testing as well as human donor, usability and animal studies if applicable) or clinical evaluation. Based on its intention and statement, for this purpose, it must generally be distinguished between different qualities of evidence which are each suitable for specific claims.

- There is visual/optical evidence, that is, any characteristics which can be assessed from a visual inspection or images relating to the device, also including technical drawings. Such evidence is suitable for the support of basic characteristics without relation to clinical effect, that is, additional colour-coding for quick identification of components.
- There is pre-clinical evidence generated with the products during pre-clinical assessment/testing which is suitable to support the technical properties of the products but again without a link to clinical performance, that is, decreased wear-rate of a new polyethylene insert in an implant as compared to the standard polyethylene in a biomechanical test setup.

- Actual clinical evidence of a device relates to the documentation of results and outcomes of the device in clinical use, with specific attention to the claim.

Clinical claim of a novelty can be substantiated if it provides evidence of its clinical superiority through trials before its implementation. Taking into consideration the amount and level of this evidence, it can be used to support any related clinical claims, that is, implant revision rates or decreased infection rates.

### *How does the clinical benefit affect the implementation of new technologies and is the clinical benefit always given?*

As with all new medical developments, the benefit/risk ratio for the patient should always be considered and be focused on what are the benefits for this particular patient group. New technologies, which would represent a major step forward in medicine (i.e. anti-microbial treatments) should, after successful and rigorous pre-clinical evaluation and soundproof of potential clinical benefits, have the possibility to enter a clinical phase without delay. This is especially important in areas where there is no satisfying treatment option yet.

But it is obvious that new technologies should not be introduced simply for their own sake, and the clinical benefit or clinical issue, that is, a better outcome for the patient or a simplified or faster procedure, must always be at the centre of attention. Hence, benefits and potential risks, for example of new materials from other engineering areas should be carefully assessed before introducing them in medical devices.

### *What extent of clinical documentation is necessary for an implant to be considered suitable as a reference implant?*

For an implant to be considered as a reference implant, sufficient clinical evidence must exist. The quality of this evidence must be based on at least medium-term clinical results (3–7 years survival analysis) or micro-motion studies on implant–bone fixation at short term (2 years). The results should be based on a standard patient, typically osteoarthritis. Several arthroplasties have good long-term gold-standard implants which have to be documented from databases/registers with sufficient completeness (10 years of survival with comparably low revision rates). It is obvious that the required survival rates for a reference implant, that is, in partial uni-condylar, in primary total knee arthroplasty or in knee arthroplasty using a rotating hinge implant or even a distal femur replacement, have to be different.

In addition, the complaint history of the reference implant has to be considered. An ideal reference implant would be supported by survival analysis over a suitable period of time, patient-reported outcome measuresa (PROMs) data from registry and/or peer-reviewed published studies, functional outcome data, clinical and other complaint histories from notified incidents, and other data sources as appropriate. The use of only one or two such sources is unlikely to give a full safety analysis.

The evidence data may also include PROMs, including functional outcomes.

### *Regulatory requirements*

Before a new or modified implant can be cleared for clinical use, its technical, biological and clinical safety and performance has to be characterised in a series of pre-clinical testing (design and material characterisation, biomechanical and biotribological testing as well as human donor, usability and animal studies if applicable). A careful and complete pre-clinical evaluation is the mandatory basis, in particular for an equivalence claim to a proposed equivalent predicate device (acc. MDR, Annex XIV, Part A, 3) followed by a formal PMCF study or sufficient clinical PMCF evidence (i.e. Implant registry data), as well as for a pre-market clinical investigation if needed (acc. MDR Annex XV).

For non-active implants for surgery, there are common basic requirements like physical and mechanical requirements for suitable implant materials, biocompatibility of materials and biological safety, sterility, expiry date and shelf life, packaging and labelling, reprocessing, MRI safety and radiological visibility.

In addition, there are particular and specific technological and clinical requirements for the intended indication (i.e. hip, knee, shoulder, etc.) based on existing standards (ISO, EN, ASTM series) and additional established test methods. Some examples are implant fatigue and endurance behaviour, fixation of mechanism between implant components (i.e. hip inserts in acetabular cup), intended range of motion, geometrical compatibility between implant components, as well as implant-related surgical instruments and roughness of surfaces in contact with soft tissue structures. Furthermore, existing test methods include the analysis of surface roughness, clearance and dimensional accuracy of articulating bearings, wear simulation (13, 14, 15, 16) and particle and ion debris characterisation (17, 18, 19, 20, 21, 22, 23, 24), sub-luxation (25), impingement, micro-separation (26), ageing resistance of polymer components (27), as well as finite element analysis (FEA)-based worst case scenario calculations to detect the relevant implant size combination for each test series.

During the last two decades, experts from all related areas, such as orthopaedic surgeons, manufacturers, test laboratories, notified bodies, research institutes, national health authorities and standardisation organisations have contributed intensively to a substantial increase in the scope and quality of today's pre-clinical evaluations.

Within the Technical Committees of International Standardisation Organisations (ISO, CEN, ASTM), a periodic review of existing standards takes place in a routine process every 5 years in relation to their individual initial publishing date. For the realisation of a new standard related to an established and well-documented test methodology, a time period of 3–7 years is necessary to undergo the initiation, drafting, harmonisation and voting process in International Standardisation Committees and related National member bodies.

Under the aspect of implant safety and performance, a major limitation is given by the required time period to create a new standard or to improve, harmonise and progress given regulatory requirements.

Looking at the acceptance criteria, today a minority of performance criteria is described in standards and a majority is based on comparative testing to equivalent predicate devices. What are the suitable acceptance criteria and results of pre-clinical testing?

Current basic, particular and specific requirements, which are based on given standards and established test methods cover only certain situations and well-known clinical failure modes and must be adapted to risk analysis and mitigation of risks considering patient factors like activity level, obesity, deformities, complex revision situations, as well as implant alignment and anatomical fit and forgivingness in clinical everyday usage. This represents a second major limitation of the current regulatory practice.

### *Evident state-of-the-art research and published up-to-date methodologies*

During the last two decades, the fields of knowledge in experimental orthopaedics, simulation, biomechanics and biotribology have developed considerably. Innovative and sustainable implants or also combinations and further optimisations of clinically proven design principles can only be pre-clinically evaluated based on a profound knowledge of biomechanics, implant biomaterials and their clinical application (surgical approaches, implant-specific instrumentation and workflows).

Therefore, the further development of suitable test methods for the characterisation of new or modified implants requires interdisciplinary cooperation between orthopaedic surgeons, research engineers, biomechanical and material scientists, biologists and the active involvement of the latest stage of knowledge about clinical failure mechanisms, retrieval analysis, adverse local tissue or related systemic reactions and increasing patient demands.

Based on a solid foundation of today's established regulatory requirements, a bridge shall be built to current evident state-of-the-art research and up-to-date testing methodologies.

In order to get closer to clinical implant behaviour and failure modes, advanced test methods like dedicated tribo-corrosion testing of implant modularities under meaningful surrounding conditions and lubricants (28, 29, 30, 31) or wear and implant modularity simulation under highly demanding patient activities (32, 33, 34, 35, 36, 37, 38), as well as sub-optimal clinical conditions such as knee malalignment or third body wear (39) are necessary to be applied.

The influencing factors for cementless or cemented implant fixation shall be examined in human donor bone studies or suitable synthetic biomechanical bone models and, if scientifically appropriate, in animal studies mimicking aspects of the clinical situation. A focus shall be on the influence of implant-bone interfaces under usage of the intended instruments for bone preparation (i.e. cavity, press-fit, migration, micro-motions, etc.) and consideration of the surgical approach and workflow (i.e. straight or angled cup inserter, intra- or extra-osseous modular revision stem assembling, etc.). In addition, the anatomical fit of the dedicated implant design and size range to anthropometric and morphometric patient cohorts (i.e. Caucasian, Asian, African), including virtual patient cohorts (statistical shape models), shall be pre-clinically examined using MRI- or CT-scan databases.

The evaluation of musculoskeletal joint kinematics and function (32, 40, 41) applying latest-stage in silico analysis methods like dynamic patient activity-based FEA simulation (42) and musculoskeletal modelling. Furthermore, augmented reality applications, artificial intelligence algorithms, and widespread retrospective clinical data files, allows for a better understanding of the expected success of an intended treatment or procedure for different patient phenotypes (cluster). In addition, the individualisation of therapies (i.e. suitability of a specific patient sub-cohort for i.e. hip surface replacement), as well as for TKA design related kinematics (cruciate retaining, medial or posterior stabilised), and TKA required soft tissue competence or degree of constraint will play a major role for innovation in arthroplasty.

Before any clinical phase of a new implant or implant-related instrument, following the pre-market clinical investigation or the equivalent device and formal PMCF pathway, it is our common understanding that all appropriate pre-clinical testing (regulatory mandatory and evident state of the art) – which has to be considered for a specific device – has been successfully completed (MDR Article 62 No. 4 Part L). Following an iterative process of pre-clinical testing alternating with the design, modification, discard of concepts and optimisation of new implants and implant-related instruments, until sound technical, biological and clinical safety evidence is given for introduction into the clinical phase.

The currently established, evident state-of-the-art research and up-to-date testing methodologies and simulation procedures in artificial joint arthroplasty have been described, voted and presented in a subsequent 1st EFORT European Consensus on Requirements for Joint Arthroplasty according to MDR 2017/745 in a progressing process prior to 22nd EFORT Annual Congress in Vienna 2021, using selected fields of high clinical relevance like orthopaedic hip, knee and shoulder arthroplasty (1). After publication, the resulting collection of the evident state of knowledge of 2021 will be a key element in substantially increasing implant and patient safety.

## Clinical requirements for introduction of new implants and implant-related instrumentation

*Regulatory requirements*

1. For any type of implant, the manufacturer needs clinical data to demonstrate safety and performance when used as intended considering different indications and patient populations. There are two possible routes to obtain the clinical data:
   a. A premarket clinical investigation according to the MDR, Annex XV. Annex XV is aligned with ISO 14155 for conducting a clinical investigation for medical devices. With the MDR those studies need to be reported, regardless of their outcome, to the Competent Authorities of the EU via the EUDAMED database.
   b. A manufacturer can claim equivalence to an already existing medical device if he is able to demonstrate full equivalence for the technical, biological and clinical characteristics (MDR, Annex XIV, Part A, 3.) of the device to the proposed equivalent device. If the manufacturer claims equivalence for an implantable device, he needs to demonstrate that he has full access to the Technical Documentation of the proposed equivalent device. In case of an equivalent device from a competitor, he must provide a contract between the two manufacturers (MDR, Article 61 No.5; MDCG 2020-5 guidance). If a manufacturer places an implant on the market based on equivalence, a formal PMCF study is mandatory to confirm safety and performance.

## Changes in MDR from medical device directive 93/42/EEC

The equivalence criterion, like approval of Metal-on-Metal Resurfacing Prosthesis, is unlikely and quite more restrictive.

Another major change with the MDR is that now Notified Bodies must conduct a pre-market assessment of all technical documentation for Class IIb implants, which is something that previously was only required for Class III devices, and which includes (as a result) a pre-market assessment of the manufacturer's clinical evaluation. Furthermore, the EU commission has installed clinical expert panels, who will review and give opinions on the assessment Notified Bodies made to manufacturers' clinical evaluations. This opinion could affect the final nature of the CE marking of the device, and it could also lead to future common specifications laying down EU-wide clinical requirements for the device in question.

The clinical expert panels have the following tasks, depending on the needs

- providing an opinion on the notified bodies' assessments of the clinical evaluation of certain high-risk medical devices and the performance evaluation of certain *in vitro* diagnostic medical devices
- providing advice to the Medical Device Coordination Group (MDCG) and the European Commission concerning the safety and performance of medical devices and *in vitro* diagnostic medical devices
- providing advice to manufacturers on their clinical development strategy and proposals for clinical investigations
- providing advice to EU countries, manufacturers and notified bodies on various scientific and technical matters
- contributing to the development and maintenance of relevant guidance documents, common specifications and international standards
- providing opinions in response to consultations from EU countries, manufacturers and notified bodies

*State-of-the-art research*

Clinical research is needed for documentation of the new implant and implant-related instrumentation to show safety and performance. The evidence shall come from well-established registers and studies including well-defined designs and sufficient number of patients.

Every claim must be evaluated like better patient-reported outcome, range of motion, reduction of dislocation, improved joint stability, etc (see also section X. Additional requirements of clinical documentation).

Proven methods like RSA, as well as new methods like observer-independent x-ray analysis for *in vivo* wear measurements and migration (43, 44) shall be applied to create objective clinical performance data in a short-term evaluation, which are predictive for long-term implant fixation.

*In silico* techniques, that is, computer simulation shall be introduced into clinical studies that are conducted

to establish the safety and performance of new medical interventions. *In silico* medicine stands for a new way to investigate living organisms and the diagnosis, treatment or prevention of disease through modelling, simulation and visualisation of biological and medical processes using computer simulations. A clear distinction should be made between single model, generic model, modelling a limited number of existing cases, and statistical modelling of a virtual human population.

*In silico* clinical trials may have supplementing benefits in current *in vivo* clinical trials. The significance of *in silico* trials depends highly on a scientifically sound verification or validation and on the data quality provided through Artificial Intelligence. For surgeons, manufacturers, notified bodies and expert panels implemented by the European Commission, the reliability and safety behind this technology are mandatory.

## When can you start using the implant routinely?

Once manufacturers receive the CE mark for a medical device, they are allowed to put it on the market and physicians can use it routinely. An implant can be used in patients routinely when a clinical investigation has been conducted to demonstrate the conformity of devices according to MDR Article 62 (general requirements) or full equivalence for the technical, biological and clinical characteristics has been demonstrated (MDR, Annex XIV, Part A, 3.) and a PMCF study has been initiated.

In some cases (i.e. when very limited clinical data is given), a controlled release of a medical device may be conducted, that is, the manufacturer only sells the device to specific clinics or countries and/or the patients involved must be included in a post-market study to extend the clinical data.

### *Requirements of clinical documentation*

Further requirements are necessary, if the manufacturer wants to generate well-designed studies including well-defined cohorts, analysed with the accepted methodology of appropriate parameters at relevant time points. They should be reported transparently (high-quality clinical data) in an early phase to prove the conclusions regarding safety and performance made within the Clinical Evaluation Report.

In general, clinical studies can be planned in a stepwise manner: After the first phase, in which the medical device is applied by clinicians who co-developed the device and are hence familiar with its usage, the second phase of clinical studies should be conducted by independent surgeons, not involved in the development of the device.

The documentation must be sufficient regarding the assessment of the safety and performance of the implant, based on a conformity assessment procedure and involvement of notified bodies (MDR Article 52 & 53), clinical evaluation consultation for certain class III & IIb devices (MDR Article 54) and mechanism for scrutiny of conformity of certain class III & IIb devices (MDR Article 55). In ongoing monitoring of notified bodies, their responsible competent authority shall review an appropriate number of notified body assessments of manufacturers' technical and clinical evaluation documentation (MDR Article 45).

Depending on the level of innovation of a medical device, a specific amount of clinical documentation is required to receive the CE mark and to regularly provide proof of clinical safety and efficacy.

The documentation must contain sufficient information for the assessment of safety and performance when used as intended by the device. In addition to a study design of high quality, this also includes the selection and documentation of appropriate parameters at relevant time points. This may include early and detailed documentation of any related complications, regular radiological controls and inclusion of relevant clinical outcome scores.

Further documentation must be collected from routine clinical use starting with the second phase of clinical studies. In addition, the collection of clinical data from independent sources (i.e. start of registry data collection) must be initiated and monitored. National or professional orthopaedic society-driven implant registries are recognised as an important source of mid- to long-term clinical results. In the future even a European-wide evaluation of outcomes, driven by multi-national registry initiatives (i.e. ISAR, NORE (Network of Orthopaedic Registries of Europe, NARA (Nordic Arthroplasty Register Association) will enhance the power for stratified analyses and extend of data collection (45). It is important to recognise that manufacturers typically obtain regulatory approval for an implant system, yet the clinical performance of individual portions of that system may differ significantly. A known example is cruciate retaining, posterior stabilised or revision knee implants of the same knee system, but of course, there are many other variants within such brand designations. These variants often have differing clinical performance in survival studies, so it is vital to the patient and surgeon that clarity exists as to whether the device described for obtaining regulatory approval relates to the particular variant being used.

The state-of-the-art documentation must be assessed by professionals with expertise within the clinical field (Notified Bodies according to MDR Article 35, Authorities according to MDR Article 45 and Expert Panels

implemented by the European Commission according to MDR Article 106).

A Summary of Safety and Clinical Performance shall be written by the manufacturer in a way that is clear for the intended user (MDR Article 32) for Class III and implantable devices and shall be made public and be documented in the European database on medical devices 'Eudamed' (MDR Article 33). All clinical data should be published on a scientific level, that is, in accepted registries and/or peer-reviewed publications from qualified clinical centres, based on well-designed studies including well-defined cohorts, analysed with the accepted methodology of appropriate parameters at relevant time points, and reported transparently.

### *Centres qualified for performing clinical studies*

In order to qualify for the performance of clinical studies, a clinical centre has to fulfil certain prerequisites, such as the provision of presupposed GCP courses for doctors, study nurses, standardised processes within the clinical test plan, required infrastructural network, a certain continuity of involved personnel, etc. In addition, they should be qualified to do well-designed studies, analysed with the accepted methodology of appropriate parameters at relevant time points, and reported transparently.

## Perspective

The recommendations underline the necessity that surgical innovation takes place with great care, with the consensus of all involved stakeholders guided by pre-clinical as well as clinical governance processes, appropriate training of surgeons and close control of outcomes.

### *The process of development of the document*

#### Inauguration workshop and preliminary recommendations

An inauguration workshop of the EFORT Implant and Patient Safety Initiative (IPSI) took place on January 21, 2020, in Brussels with the participation of a steering group invited by the EFORT Board. The steering group consisted of clinical experts, scientists, representatives from implant manufacturers, regulatory authorities and patient organisations. Also attending were representatives from European National Societies and Speciality Societies, who were identified before the initiative commenced.

The key questions about pre-clinical and clinical requirements for the introduction of new implants and implant-related instrumentation were discussed. Moreover, questions on degrees of novelty and innovation


**Figure 1**
Overview of key tasks and major steps in preparation of the 'EFORT IPSI Recommendations WG1 on Introduction of innovations in artificial joint arthroplasty' (blue) and interaction with the '1st EFORT European Consensus on Medical and Scientific Research Requirements for the clinical introduction of orthopaedic joint replacement devices' (green). Convenors and co-authors integrated the comments from the steering group and the National and Speciality Society representatives into the final version.

were discussed and when an implant and implant-related instrumentation can be used routinely. It was agreed that the target audience for these recommendations will be primarily European orthopaedic surgeons, researchers, experts from implant manufacturers, regulatory authorities and patient organisations.

After the inauguration workshop, the relevant questions have been translated by the convenors in dialogue with the co-authors and workshop participants in key areas as fundament to develop the recommendations.

### Consultation of Steering Group, National and Speciality Societies

Draft V1 was circulated for critical review and further input to the co-authors and the WG1 steering group on July 8, 2020, by the EFORT office. In close dialogue with the EFORT board, the convenors of IPSI WG1 distributed draft V2 on October 1, 2020, via the EFORT Office to the workshop group members as well as to EFORT National Member Societies and Speciality Societies (National Delegates and Presidents of Speciality Societies), to receive additional input from clinical, scientific and regulation experts.

In total 27 steering group members, 75 National Delegates and 3 speciality Societies Representatives were contacted, and we received 53 responses (51%). Detailed feedback was obtained from WG1 steering group members and from BVOT Belgium, DOS Denmark, SOFCOT France, SIOT Italy, NOV the Netherlands, NOF Norway, SOA/ZOSZD Slovenia, Swiss Orthopaedics Switzerland and BOA United Kingdom.

The main topics of the recommendations and the survey results are presented at the 22nd EFORT Annual Congress on June 30, 2021 (Fig. 1).

**ICMJE conflIct of interest statement**

SO is a board member and Scientific Chair of EFORT and also a chair of the EFORT Implant and Patient Safety Initiative (IPSI) WG 1 'Introduction of innovation'. TGR is a chair of the EFORT Implant and Patient Safety Initiative (IPSI) WG 1 'Introduction of innovation'. SO, TGR, LC and MJ are Scientific Committee members of the 1st EFORT European Consensus. KPG is a board member and Past President of EFORT (2020–2021) and also a board member of the German Society of Orthopaedics and Traumatology. RGHHN is currently Secretary General of EFORT (2021–2023). TGR and SR are employees of Aesculap AG Tuttlingen. SO, TGR, SR and KPG all received logistic help and staff support for organisation of the consensus conference from EFORT, and support from the Medical Faculty at the University of Dresden for infrastructure (room and audio-visual cost, staff support) for the organisation of the consensus conference (unrestricted educational grants). The authors declare no conflict of interest relevant to this work.

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