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EDITORIAL

# The era of phased introduction of new implants

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At present, most new designs for total knee (TKP) and total hip prostheses (THP) are approved and distributed on the market without extensive safety and effectiveness testing via the 510(k) pathway in the United States and regulation via notified bodies in Europe (Directive 93/42/EEC).[1,2] In 2007, the European Union reclassified total hip, total knee and total shoulder prostheses to "class III medical devices" (Directive 2005/50/EC). Class III medical devices are high risk and require pre-marketing testing in patients.[3] Nevertheless, the 510(k) pathway in the United States and the reviews of device reliability via notified bodies in Europe have created an environment in which unsafe TKP and THP can reach the market.[4] This lack of adequate regulation has led to the widespread use of potentially unsafe TKP and THP, with failure rates two to ten times the standard of national joint registries (i.e. 5% failures at ten years follow-up).[2,5-10] Furthermore, problems with new methods of fixation of orthopaedic implants such as Boneloc cement (Biomet Inc., Warsaw, Indiana), have also resulted in revision rates that were 14 times higher than normal.[11] Taking the above into consideration, the selection of any new implant, fixation method but also new surgical technique should be evaluated to have the optimal patient safety. The IDEAL consortium is an important proponent of this.[12] Do the potential advantages of new techniques outweigh the potential risks?[13]

To ensure quality of orthopaedic implants, and thus patient safety, a phased evidence-based introduction, as is common for pharmaceuticals, is needed to regulate the introduction of new TKP and THP to the market.[12,14,15] Some initiatives have already been proposed.[12,16,17] A phased evidenced-based introduction will very likely encounter three categories of implant failure:

- expected and early detected failure modes;
- expected and late detected failure modes;
- unexpected failure modes.

Expected and early detected failure modes are discovered some time before or around the time they actually happen and they can thus be evaluated in a pre-market setting of a phased evidence-based introduction. However, expected and late detectable failures are discovered when, or shortly before, they happen and can be detected in a pre- and post-market setting depending on the duration of the pre-market phase and the timing of the failure. If they happen in the medium-term to long-term follow-up, detection in the post-market phase is more likely.

The same applies to unexpected failure modes. These present in both the early pre-market and late post-market phase, depending on failure mode (e.g., biological response (such as pseudotumours) and material breakdown (such as modular femoral necks)). In general, the longer the pre-market phase, the higher the likelihood unexpected failures will be detected.

The unexpected failures stress the importance of national implant registries with high completeness ratios, as well as the collaboration between national registries as is advocated by ICOR (international consortium of orthopaedic registries), NARA (Nordic Arthroplasty Registers) and NORE (Network Orthopaedic Registries of Europe). Although these large registry databases are an important method of detecting implant failures (i.e. the signalling function), they are only available at mid-term or later follow-up after inclusion of tens of thousands of patients.

Regarding expected and early detectable failures, this month in *Bone & Joint Research*, Malak et al[18] report a systematic review on surrogate markers of long-term outcome in primary total hip arthroplasty (THA). They find that RSA and EBRA measuring implant migration and wear are validated surrogate markers for long-term primary THA outcome and propose RSA in the pre-market testing of new prostheses. These results confirm those of previous studies.[9,19-24] However, the authors leave us wanting in answer to the

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important question: what thresholds should we then use for an acceptable implant migration and what is an acceptable wear rate? Predefined reliable threshold values, which determine acceptable and non-acceptable implant-bone migration and articulation wear rates, ideally derived from systematic reviews, are prerequisites for a phased evidence based introduction of new implants and to distinguish between good and poorly performing implants. Such thresholds should, however, not be set in stone. They require regular update, validation and refinement.

An analysis of the risk of bias on the included studies would also have been helpful to interpret the results of Malak et al.[18]

In the absence of proper blinding, incorporation bias could have confounded the results of individual studies, as patients with high migration or high wear may be more closely monitored and, when presenting with symptoms, may be more likely to be offered a revision procedure compared with patients with no migration or very low wear. In the latter, the lack of migration and wear may be reassuring to both physician and patient, thus precluding a revision. These patient scenarios, (caused by a lack of blinding), work as a self-fulfilling prophecy potentially to overestimate the accuracy of predicting outcome of revision or no revision based on (early) migration or wear.

Competing risks are another potential source of bias. For example, risk of death of the patient competes with revision of the component. Thus the procedure of interest (in this case revision) may not be performed, even though there is significant aseptic loosening or wear. In other words, if the prosthesis outlives the patient, one cannot accurately determine the revision rate without performing a competing risk analysis.[25,26]

This has important consequences for the 'generalisability' of predictions based on early migration or wear. The accuracy of these predictions tends to be overestimated in patient populations with decreased life expectancy or higher risk of revision for other reasons than interest as false-negatives (i.e. no revision predicted but revision would have happened) are obscured by the competing event of death or revision for another reason.[25,26]

Nevertheless, there is a large body of evidence indicating that early migration measured with RSA can be used in a phased evidence-based introduction of TKP and THP.[9,19-24] The study by Malak et al[18] confirms these studies and also includes wear to the palet.

In regard to expected and late detectable failures, we should strive to detect them as much as possible in the pre-market phase, but we should at the same time accept that they also occur in the post-market phase. These expected and late detectable failures include, among others, revision for septic loosening, peri-prosthetic fractures, revision for dislocation, pain, or osteolysis, pseudotumours and prosthetic hip-associated cobalt toxicity (PHACT).

Regarding unexpected failures, the metal-on-metal hip arthroplasties have introduced previously unexpected failure mechanisms of pseudotumour formation and PHACT. It is, therefore, wise to anticipate that a new design can introduce unexpected ways of failure. These unexpected failures are not limited to complications regarding the prosthesis, such as loosening or dislocation, but may also entail more generic medical complications or symptoms such as PHACT with metal-on-metal THA. Unexpected failures require vigilance from surgeons and national joint registries alike. The signalling function of national joint registries, detailed case series and cohorts is of paramount importance for identifying these unexpected failure modes.

When taking the above into consideration, it is clear that it is a challenge to design a phased evidence-based introduction of a new prosthesis that examines every possible mode of expected and unexpected failure. However, from a realistic point of view, it is possible to include the expected and early failures and, to some extent, the expected and late failures in a phased evidence-based introduction. This is already happening for knee arthroplasty – RSA-tested TKP have a 22% to 35% reduction in revision for any reason compared with non-RSA-tested TKP in several national joint registries.[27] We can only imagine what formal phased evidence based introduction can do. Furthermore, post-marketing surveillance in national joint registries and good-quality reports of case series and cohorts of a particular prosthesis, as well as patient series, will cover the unexpected and remainder of the expected and late detected failure modes.

The question that we should ask ourselves now is if we want to continue with the current chaotic introduction of a new prosthesis,[28] which has proven to be unsuccessful and even harmful to patients,[28] or should we adopt an early version of a phased evidence-based introduction of new implants, which has been proven to be successful?[27] It is very likely that a phased evidence-based introduction of new implants and fixation methods will have an evolution of its own before a final optimal-phased introduction programme, including not only implant-bone fixation (i.e., RSA and EBRA) but also biological response and patient outcome measures.[29] Nevertheless, as Karrlhom[20] noted, fast spread of undocumented new implants should be part of orthopaedic history. At present, any phased evidenced-based introduction is better than the chaotic introduction, which will also provide experience and data in order to develop better systems in the future. One may even go as far as stating that evidence-based introduction of new TKP and THP is more likely to reduce the revision burden within the next decade than the introduction of any new design feature.[17] We are thus at the dawn of the era of phased introduction of new prostheses. And so, when do we start?

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