# Reducing potential nanotoxicity of orthopaedic implantable devices

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**Introduction:** Integrating data services across the spectrum of the life sciences illustrates the design and development of novel therapies in terms of Translational Research (TR) paths. The aim is to build a ‘Commons’ registry from multiple centres by allow for open archiving of key characteristics of materials used in the preparation of implantable devices. This should potentially identify pitfalls associated with the use of certain materials for specific biomedical applications and alert the community of the potential risks before they occur. There is a perceived clinical need for better ‘upstream’ understanding of factors that may lead to clinical problems, This relates in particular to orthopaedic implants, whose unanticipated nanoscale issues have clinical consequences. It is relevant to all implant types(1).

Table 1 LIST OF Some of the tests that are currently analysed, after Marquis et. al. (2009) Analytical methods to assess nanoparticle toxicity. Analyst, 134, 425

The aim is to present a set of relevant variables and their parameters that can be collected from different sites to collate the potential values and risks associated with new materials which potentially offer great advantages – especially with respect to their electrochemical properties. Sharable collaborative datasets, such as the UK *National Joint Registry (NJR)* for implants but characterizing the use of materials; should consider all available knowledge of their ‘through life’ cycle, minimizing the risk of developing future potentially adverse bioactive agents.

**Methods:** The challenge we currently face is in the management of information regarding new devices that have potential strengths and weaknesses. With new materials and the associated manufacturing processes, there are a myriad of variables that need to be considered. Ultimately we are aiming for the optimum end result in terms of safety and effectiveness through ‘Longevity’ of implantable devices. There are some materials which are completely inappropriate such as compounds containing heavy metals (*e.g.* Mercury), which should be ‘red flaged’ and never be considered and then those which are currently in use which are controversial, such as devices shedding Cobalt and Chromium particles which are known to be genotoxic.

Conversely, tried and tested materials such as Ultrahigh Molecular Weight Cross-linked Polyethylene and certain ceramics, which has stood the test of time, albeit with some issues around loosening of orthopaedic implants, but it is generally safe. We have learned that certain materials can be protected with respect to their biological interface, such as a silver (*Ag*) coating to decrease the risk of bio film formation, but we are still faced with a disjointed picture with respect to understanding how these new nano technologies impact on biology and what can be done to make the best of their potential. The following qualities and their assay modes are relevant (*Table 1*).

|  |  |  |
| --- | --- | --- |
| Assay type  | Process probed  | Assay  |
| Viability  | Metabolic activityProliferationNecrosisApoptosis | MTT, Alamar BlueTotal DNAMembrane permeabilityAnnexin-V, TUNEL |
| Mechanistic  | Oxidative stressDNA damage  | ROS detection TUNEL |
| Functional/ Behavioural  | DifferentiationInflammatory responseECM formationCell mobility/recruitment | RT-PCRELISAAlizerin Red, CollagenTrans well plates, scratch test  |
| Cellular uptake  | Endocytosis Phagocytosis  | FRAPTEMQDs |

Society cannot yet know the optimum approach; since there are presently no preclinical testing methods that can reliably predict outcomes. There is still a need for empirical data to be analysed and to date, registries provide the best approach.

As expectations arise within society for an improved longer term quality of life, greater pressure is placed upon healthcare providers and industry to deliver potential new solutions. Our knowledge base can therefore be categorised according to the "Rumsfeld Paradigm" which refers to what the professions recognise and what information is potentially available that could be of value.

Broadly speaking this relationship between local and remote (other centre’s) perspectives on information about materials, can distinguish what we know that we ‘need to know’ from empirical processes, *i.e.* results of current tests and registries that have been evaluated (2). What we don't know that others know, *i.e.* information that is ‘out there’ from different sources including prorietary databases that hold intellectual property securely in industry, and things that we ‘know’ that are ‘unknown’ (KU). The latter includes the information that registries can provide us with. These also include case series, and potentially drive further registry development, integrated with failed device ‘Retrieval’ information – ‘Unknown Knowns’(UK). The adaptation for a ‘Creative Commons’ approach could rapidly progress this process ensuring legal protection through appropriate licencing (3).

The last category is the "unknown unknowns" (UU), where there may be future tests. The clinical outcomes will ultimately provide information needed to reach sound conclusions, but at the moment this is not yet in existence. These may relate to the consequences of higher levels or to clinical examination through modalities such as Magnetic Resonance Imaging (MRI) or Ultrasound Scanning (USS) or multimodal imaging. Whatever the technology or technique, the question is how to inform the process of future implants design.

Since there are no long-term evaluations at this stage, the question is also one of whether there are reliable and robust short-term post-implantation surrogate measures which can predict failure, as has successfully be seen with Radiostereometry (RSA) which can demonstrate significant wear in some implanted prostheses, using bearings such as ultrahigh molecular weight polyethylene.

Since ion levels (Nanoparticles between 100-120 *nm*) does not clearly correlate with failure of implants, either through mechanical failure or potential risk(4), and being based on data from ‘retrieved’ specimens, this represents the ‘known unknowns’ that actually do not yet answer the critical question; ‘*Is this a reliable indication of risk?’* It illuminates the fact that there is presently no more thorough way of predicting implant success *ex-vivo.*

**Discussion:** With altering public perceptions, reported problems on metal-on-metal (MoM) bearings potentially will challenge the development of new devices through failure to disaggregate the information regarding failing implants from others that use similar materials. Whilst history advises caution with respect to new prostheses, and some MoM devices have raised concerns, though apparently it is only certain types of bearing that precipitate the problmes. It is population groups, providing epidemiological data through registries in this countries such as Australia and the UK that offer usable results for specific devices. Attempting to extrapolate from one to another is however potentially flawed. Ideally if rigorous *in-vitro* analysis could offer new and reliable tests, these would be of value though they are unlikely to predict the local biological environment including the sinovial (natural joint lining) cells and their interaction with the prostheses.

Since we are aware of certain metal debris from the modular hips, it is unrealistic to assume that this relates specifically to other reported devices that have been seen to have higher failure rates, such as the ‘Duron’ cup and ASR hips which have already been withdrawn from the market in 2010.

The question then arises; what new paradigms, with associated controls, can be employed to improve our perception of potential new materials for biomedical applications, assisting society in stopping vulnerable designs from being implanted early in the process, without having to go through extensive expensive and risky clinical trials. Registries will therefore be of value in avoiding the designing of future implants which steer society down a ‘*cul-de-sac’*.

Clearly it is reasonable for regulatory agencies such as the Food and Drugs Admininstration (FDA) and European Medical authority (EMA) to step in if there is irrefutable evidence of catastrophic failure. Fortunately however, across the spectrum of implantable devices these are rare. Unfortunately as rare as highly successful technologies are, in effect they are seldom bio inert. The issue is the middle ground, where we must first address issues of how we analyse the complexity to ensure that salient features are recorded simply within databases and those features, which have been demonstrated to be identified as ‘not fit for purpose’, and so can be quarantined from future design processes.

As nanotechnologies develop, this negative aspect will need to be addressed so as to avoid the taint by association of a potentially very valuable industry.

The proposed method would be considering the ‘chain of evidence’ in a similar way to but the inverse of considering ‘chain of error’. This positive aspect considers both the data collected across the life-science spectrum from different areas of basic science right through to the process of design, development and clinical testing, industrialization and commercialisation, in terms of technology transfer. It is not unreasonable to consider that such an evidence path is demonstrable when seeking future regulation regulatory approval, however it still has to be recognised that this only accounts for the ‘known knowns’ (KK) and ‘unknown unknowns’ (UU) may be accessible through data mining. We are unfortunately left with the situation where to develop a predictive loop for future realisation; both the ‘unknown knowns’ (KU), the ‘known unknowns’ (KU) from registry information will have to plug the gap and hopefully diminish the ‘unknown unknowns’ (UU) which can jeopardise future technological progress.

**Conclusions:** Through machine learning, there are techniques available to predict these and should be applied to the registries using specific evidence models which can be primed by data from industry. At the same time, dissemination of established information should minimise the risk of future harm through rapid dissemination of results which are validated.

The development of a robust Translational Research (TR) approach (5) should therefore precede the clinical implementation of future materials.

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| --- | --- | --- |
|  | *Known* *By community* | *Unknown**By community* |
| Known by user | **Known Knowns (KK)**Information that we have access to *such as table 1*  | **Unknown Knowns (KK)**Information that we do not yet have access to but could seek permission for  |
| Unknown by user | **Known Unknowns (KU)**Information that we have access to  | **Unknown Unknowns (UU)** Information that may be very relevant but which is not ‘on the horizon’  |

Table 2 ‘Rumsfeld's’ Paradigm

**References:**

 (1) Art Sedrakyan. Metal-on-metal failures—in science, regulation, and policy. Lancet 2012 Mar 13;379(1174):1176.

 (2) Alison J Smith *et al,* on behalf of the National Joint Registry of England and Wales. Failure rates of stemmed metal-on-metal hip replacements: analysis of data from the National Joint Registry of England and Wales. Lancet 379, 1199-1204. 13-3-2012.

 (3) Creative Commons Licences. 22-5-2012. www.creativecommons.org/licences

 (4) Daniel J *et al*. The validity of serum levels as a surrogate measure of systemic exposure to metal ions in hip replacement. J Bone Joint Surg Br 89-B[6], 736-742. 2007.

 (5) Miles-Board *et al*. Extending the role of a healthcare digital library environment to support orthopaedic research. Health Informatics Journal, 2006;12(2):93-105.