Metal on Metal bearings: Evaluation of the Potential Risks in Clinical Use and the associated data management issues challenging prospective risk analysis

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Introduction: Integrating data services across the spectrum of the life sciences would illustrate the design and development of novel therapies in terms of translational research (TR) paths. This would potentially identify pitfalls and alert us before they occur. Exemplified by the current 'state of the art' virtual collaboratory prototype, where there is a perceived clinical need for better 'upstream' understanding of factors that may lead to potential clinical problems, we refer to current experience with a novel 'bearing' in an orthopaedic implant, whose unanticipated nanotechnological issues have clinical consequences. The aim is to develop a consensus opinion for minimum sharable datasets, characterising the use of materials; so as to consider all available knowledge of their 'through life' cycle, minimising the risk of developing future potentially adverse bioactive agents.

In the domain of musculoskeletal science, there are rapid advances in both the information technologies to support and monitoring clinical services, and also the underpinnings in basic science, such as biomechanics. The issue is that nanotechnological changes do have an impact on the clinical scale. An example of this is demonstrated by one of the most important evolutions in the last decade in total hip arthroplasty (replacement) with the re-emergence of the use of 'metal on metal' (MoM) bearings, as a solution to treat young patients with end stage osteoarthritis.

This is not a new concept, having been introduced in every decade since the 1950's with varying clinical success. The introduction of large head MoM resurfacing in the 1990's led to a huge increase in its use, in total hip arthroplasty. Potential clinical advantages have been developed alongside a greater understanding of the ways these bearings work, including the final stages of 'machining' once the prosthesis has been implanted. The results of clinical success of these implants have been variable between centres, and between different implants. The Birmingham hip resurfacing has recently published excellent ten year outcomes, providing a reliable marker of longevity. Another implant, the ASR total hip was withdrawn from the market due to unacceptable failure rates, suggesting that optimal design remains serendipitous.

Concerns raised with metal on metal bearing relate to metal ion production, potentially causing toxicity, hypersensitivity, carcinogenicity (cancer inducing) as well as osteolysis (bone eroding) and the development of pseudotumours in some individuals. While all these issues have been raised, the data in the literature is very confused and difficult to interpret or transfer between research studies. It is mainly retrospective analysis, rather than being anticipated and prepared for.

Methods: *The perceived need for developing Virtual Research Environments:* Implementation of novel scientific discoveries in biomedicine therefore depends on the ability of researchers and clinicians being able to collaborate. The introduction of the research governance framework in the beginning of the 21st century, after the implementation of such MoM devices heralds reforms in healthcare research management that tighten regulations, reducing the risks of avoidable errors, but in turn risk alienating many contributors due to the greater exposure to regulatory burden. Our aim therefore is to manage this, ensuring quality and facilitating translational research. Quality Improvement (QI) in research management may be achieved through Virtual Research Environments (VREs), bridging clinicians and basic scientists, who are conducting research studies, enabling them to collaborate in sharing and reviewing components of internet managed trials.

The aim of creating the Virtual Research Integration and Collaboration (VRIC) environment was to develop a VRE to enable Translational Research at the Royal National Orthopaedic Hospital Trust (RNOHT). Taking advantage of Web 2.0 technologies, the prototype VRIC provided scientists with tools that facilitated collaboration during the conduct of research trials. Through integrating a structure to manage governance, the VRE simplifies the process of overseeing compliance of a trial with the established policies.

The dedicated study management portal supports associated documentation and workflow management of a generic research trial. This was not prepared specifically for the review of MoM, rather, inspired by the challenges that such novel technologies can impose clincally, originating from a nano scale.

VRIC (1) is composed of a trial section and a repository to store the documents (text files, video, data files) related to a trial, which are relevant to the research team. A collaboration section allows researchers to manage virtual conversations regarding their projects; and a contacts section creates and maintains the VRE community. Implementation of the suggestions from early adopters and finally an evaluation of the impact of the solutions on the participants' work practices (in line with research by Steen(2)), meant that the results of the evaluation are 'fed back' to the development team and integrated into the system.

Results of using a VRE: Ten major projects, led by users ranging from University undergraduate students to senior lecturers and professors, tested VRIC. This involved projects with National and International funding. Researchers involved in these trials use the VRIC tools to manage aspects of their studies in various ways, from sharing data to discussing results and organising publication of their studies. Interviews

conducted with this community of end-users provided feedback from the system. Analysis of the interviews provided the development team with insight into the advantages that VRIC offered to the hospital, highlighting the importance of providing technical training to medical staff. The studies evaluated the use of the system for clinical follow-up and potential integration into monitoring new devices through to established registries.

Discussion: The potential role of linking basic science to clinical discovery is where VREs come to the fore. Although in the exemplar of MoM, trace elements such as cobalt, chromium and molybdenum are present in individuals with no artificial metal devices fulfilling essential roles in metabolic function, increased metal ion levels are well documented in subjects using metal on metal bearings. Few studies however agree on the correct method of sampling; whether serum, red blood cells, urine or whole blood levels should be used. There is further confusion with different studies reporting different units. Such standards, if agreed, would ensure data collection methodologies that are compliant. More recently it has been suggested that monitoring should be done using 'parts per billion' units. Daniel *et al* (3) questioned the use serum levels and suggested whole blood levels as a measure of systemic exposure to ion levels.

Even with such an agreement, we don't yet know how to use this information. There is no agreed 'safe' level for cobalt and chromium levels, and when levels are high there is no concensus as to how to proceed clinically, particularly in individuals with clinically well performing prostheses, suggesting the adoption of Bayesian statitical models in the evaluation.

VREs (4-6) may offer a better chance of correlating disparate datasets. At this present time the causes of elevated metal ions is also unclear. Hip simulator studies have shown a number of factors which influence this. These include smaller head size, increasing modularity and the overall position of the implanted components. These simulator studies may not represent *in-vivo* conditions. There may be device related issues causing higher ion levels. Some models of implants appear to be more forgiving than others in terms of malposition and FEA models are exploring this. Data assimilation across disciplines would help provide new insights.

Pseudotumours have also been a controversial issue when discussing MoM bearings. These are large focal solid or semi liquid lesions in the absence of neoplasia (cancer) or infection. Since the incidence of these is 0.1-3%, differing between institutions, it has been difficult collect the information required to identify the high risk groups, through accumulation of studies (metanalysis) and examination of joint registry data, so linking in to registries would assist with this.

Conclusions: While the problems related to the use of metal on metal implants are well documented, it has taken a long time to recognise some of these issues. This remains retrospective analysis. The potential benefits of considering 'through life' cycle analysis before clinical implementation are clear. With the widespread use, and differences in measuring outcomes as well as numerous small studies, it still challenges collation, analysis and interpretation of information. The poor performance, and high rates of side effects in some centres, by some devices and by some surgeons may even see the total abandonment of the device's use, which we believe could be avoided by better compatibility and transfer of data between institutions.

The rules of governance are changing. They are necessarily becoming more stringent as interventions offered to treat conditions carry unpredictable side effects, often associated with novel therapeutic vectors. The clinical relevance of this relates to the obligations of those involved in research, to ensure the best protection for subjects whilst encouraging the development of the field.

Existing evidence supports the concept of e-Governance in operational health research and in the strategic domain of policy formation, building on the impact of the UK Comprehensive Research Network and recent EU Directives. It is now also necessary to focus on the issues of regulation for Advanced Therapeutic Medicinal Products (ATMP). Technology research and plans must therefore develop in close association between tissue engineering and treating clinicians, learning from these bioengineering examples. The scope of this strategy relates to the handling of human tissues, their transport and the storage of specimens in accordance with current EU directives and the Human Tissue Authority (HTA) regulations.

The added value of VRIC to the community comes from having the tools to support the peer review. VRIC is intended to become instrumental in training the future generations of musculoskeletal scientists and other communities of students, which would benefit from the advantage of co-learning with peers in the field of translational research. VRIC provides a context for asynchronous collaboration, whilst conducting trials is simplified by means of technology. Future work involves rolling out the applications within different overlapping jurisdictions to support secure collaboration between these 'walled gardens', offering tools to support the nanotechnology indsutry both directly and indirectly.

References:

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