Institution: University of Strathclyde

Unit of Assessment: 3

Title of case study: Evaluation of the biological safety of metal-on-metal hip resurfacing implants leads to health benefits for patients

1. Summary of the impact (indicative maximum 100 words)

Research at Strathclyde University, led by Professor Helen Grant, provided data that contributed to the withdrawal of the DePuy ASR™ metal-on-metal hip resurfacing implant from the market in September 2010. This withdrawal was based on the increased rates of failure, due mainly to release of metal ions from the cobalt-chrome alloy implant into patients' blood circulation. Over 93,000 patients are affected worldwide. The impacts of the research were (i) clinical - with concerted focus on patient health, removal of implants if required, prevention of long term metallosis; (ii) procedural - a reduction in the use of metal-on-metal implants more generally in the UK and worldwide, decline in use of metal-on-metal articulations, and renewed focus on regulation of orthopaedic implants; and (iii) economic - income to patients who have successfully sued the manufacturers.

2. Underpinning research (indicative maximum 500 words)

Context:

The ASR™ acetabular system hip resurfacing implant made by DePuy International Ltd, which was widely used in younger patients, was made of cobalt chrome alloy, and it failed because of pain, swelling around the hip, and deteriorating hip function caused by release of metal ions cobalt (Co) and chromium (Cr), locally, and into patients' blood circulation. The work in Strathclyde was instigated in 2006 when Professor Grant's research on metal-induced toxicity came to the attention of Dr Allan Ritchie, then Global Head of Research & Development, DePuy International, during a visit to Strathclyde University. He brought the leaching of Cr and Co ions from metal orthopaedic implants to the attention of Professor Grant, and arranged sponsorship of PhD student research project to initiate the investigations. Since then, researchers at Strathclyde have found that blood metal ions were elevated in patients with ASR implants, and peripheral circulating lymphocyte numbers were decreased. The toxicity of Cr and Co ions to cells in vitro was demonstrated [3, 4, 5], furthermore, Co and Cr ions were released from ASR wear debris implanted into mice, and the cobalt ions in particular disseminated into the blood and into organs of the mice [2]. The work was a significant part of a large body of research in this field in the UK and elsewhere that brought about the withdrawal of the implant, however the Strathclyde team were the first group to show dissemination of metal ions from ASR wear debris in an animal model, and to demonstrate the mobility of the cobalt ions, and their clear uptake into organs.

Key findings:

- Chronic exposure to Cr (Cr VI), at concentrations measured in the blood of patients with metal-on-metal (MOM) orthopaedic implants, caused toxicity to both osteoblasts and monocytes in vitro (Reference 5). Biomarkers showed the mechanism involved oxidative stress.
- Distribution of Cr in patients' blood was measured; workers at Strathclyde found that circulating metal ion levels should be measured in whole blood, rather than in plasma/serum (Afolaranmi et al 2008). This finding influenced the design of many parallel studies world-wide. Two clinical studies were carried out in the Southern General hospital, Glasgow, funded by DePuy, with consultant surgeon Mr Dominic Meek and his team. Patients with ASR implants showed high circulating Cr and Co in their blood post-operatively (6 months to 2 years). Co levels were elevated particularly at 2 years post-operatively. (Afolaranmi et al, conference paper at the British Orthopaedic Society, Newcastle, 2009)
- Patients with ASR implants have decreased numbers of both circulating total white blood cells, and subpopulations of B lymphocytes in their blood 6 months to 2 years postoperatively, when compared to their own pre-operative numbers.
- Cr and Co ions were toxic to freshly isolated human lymphocytes in vitro, causing apoptosis [3].
- Cr levels were measured in a pseudo-tumour, and data published in the US Journal of Bone & Joint Surgery (2008) – this helped bring the work to the notice of USA clinicians [6].

- ASR wear debris implanted into mice caused a local inflammatory reaction, strong recruitment of macrophages/monocytes, granuloma and fibrosis [1]. Expression of inflammatory genes was induced. The wear debris released Cr and Co ions into the animals' blood. Co was a mobile ion, and was found in all organs analysed – liver, heart, brain, testes, kidney and spleen. Released Cr was not disseminated significantly through the body [1, 2].

Key Researchers at Strathclyde:
MH Grant, Professor of Bioengineering University of Strathclyde, acted as PI/Supervisor throughout. Dr J Brewer, Reader in Strathclyde Institute of Pharmacy and Biomedical Sciences between 2007 and 2010 advised on immunology. Dr J Tettey, Lecturer in Strathclyde Institute of Pharmacy and Biomedical Sciences, in 2005-07 helped set up analytical methods for metals.

3. References to the research (indicative maximum of six references)

[1] Akbar M, Fraser AR, Graham GJ, Brewer J, Grant MH. Inflammatory response to cobalt chromium orthopaedic wear debris in a rodent air-pouch model. J. Royal Society Interface, 2012; 9 (74) 2109-19. [Note: Included in REF2 submission for UoA3]

[2] Afolaranmi GA, Akbar M, Brewer J, Grant MH. Distribution of ions released from cobalt and chromium (Co-Cr) alloy orthopaedic wear particles implanted into air pouches in mice. J. Biomed. Mater. Res. 2012; 100(6) 1529-38.

[3] Akbar M, Brewer J, Grant MH. The effect of chromium and cobalt ions on primary human lymphocytes in vitro. J. Immunotoxicology, 2011, 8(2) 140-149.

[4] Raghunathan VK, Grant MH and Ellis E. Changes in protein expression associated with chronic in-vitro exposure of hexavalent chromium to osteoblasts and monocytes: a proteomic approach. J Biomed Mater Res. 2010; 92, 615-25.

[5] Raghunathan VK, Tettey JNA, Ellis E and Grant MH. Comparative chronic in vitro toxicity of hexavalent chromium to osteoblasts and monocytes. J Biomed Mater Res. 2009 88 543-550.

[6] Clayton RAE, Beggs I, Salter D, Grant MH, Patton JT and Porter DE. Inflammatory pseudotumour causing femoral nerve palsy two years following metal on metal resurfacing of the hip. A case report. J. Bone Joint Surg. Amer. 2008, 90 1988-1993

Other evidence for quality of research
This body of research has been the subject of rigorous peer review by the Journal editorial boards. The research was funded directly by the implant manufacturer, DePuy International, and by an EPSRC Case award with the company. The work has been widely published and presented at conferences, both as peer reviewed communications and invited talks in the UK and in Europe.

4. Details of the impact (indicative maximum 750 words)
Process & events from research to impact:
The Vice President Research & Development at DePuy International [Source A] brought the leaching of metal ions from metal orthopaedic implants to Grant's attention in 2006. The research was then funded by DePuy (2006-2011) and the results directly disseminated to them at regular 6 monthly research meetings (September 2007 – March 2011). The main collaborator was Mr Dominic Meek, consultant orthopaedic surgeon, Southern General hospital, who provided access to patient samples, and advised on all clinical aspects of the work [Source B]. Professor Helen Grant initiated and was PI on the project, developing it from her interest in toxicology of metals. The main industrial collaborator at DePuy HQ, at Leeds, at the most crucial time (2009-2011) was Professor Graham Isaac, Senior Engineering Fellow (Hips), who had direct responsibility for design and monitoring of hip implants for DePuy International [Source C].

All project data was transmitted by transatlantic telephone conference to DePuy scientists and lawyers in USA, in addition to our industrial collaborators in Leeds. We summarised all data on

- ASR patient blood levels of cobalt & chromium compared with other implants;
- Levels of circulating white blood cells and subpopulations of lymphocytes in patients with

ASR and other implants
- Dissemination of cobalt & chromium ions in mice that had received ASR wear debris implants
- Expression of local inflammatory markers in response to ASR wear debris
- Toxicity of Co and Cr ions to human lymphocytes in vitro.

Mr Meek also received the data; attended meetings with the team from DePuy, and disseminated information to colleagues at professional & clinical meetings. Professor Grant presented data at a meeting on safety of metal orthopaedic hips, to a group of UK orthopaedic surgeons and implant manufacturers in June 2008. This initiated multi-centre discussions among surgeons on the importance of metal ion release. The Strathclyde data on blood metal ion levels in patients and the effect of kidney function on metal accumulation was presented at the British Orthopaedic Society in September 2009, and discussed with surgeons directly.

Furthermore, Prof Grant was a member of MHRA (Medical & Healthcare Regulatory Authority) Expert Group on the Biological Safety of Metal Orthopaedic implants (2006- 2010), and took an active part in the committee meeting that agreed on the safety cut-off level of 7 µg/l for either Co or Cr ions in the blood of patients with ASR implants as quoted in MHRA Medical Device Alert MDA/2010/069. This committee was attended by several orthopaedic surgeons, who transmitted the discussions directly into practice, disseminating the information rapidly to their clinical colleagues, via the professional societies, British Hip Society & British Orthopaedic Society [Source D].

Types of impact:
- Impact on the DePuy company's commercial decision making.
- Impact on patient health: concerted focus on patient health, removal of implants if required, and prevention of long–term metallosis.
- Impact on NHS policy: with renewed focus and understanding of risks involved, the Medical and Healthcare Regulatory Agency, the device regulatory authority, has continued to investigate the biological safety of metal-on-metal (MOM) implants issuing guidelines and updates.
- Influence on hip replacement design: awareness of the release of metal ions from MOM implants led to a general decline in this type of articulation, not just the DePuy ASR^{TM} design
- Economic benefit for patients successfully suing the DePuy company

Impact on DePuy: The research findings were discussed with DePuy at six month intervals. DePuy International recognised the problem of metal ion release from the ASR implants, and acted to withdraw them from the market, limiting the damage and thus avoiding a larger scale incidence of adverse effects worldwide. The company issued a voluntary withdrawal notice on 24 August 2010 taking the ASR device off the market immediately [Source E]. The use of ASR implant first declined, and then completely stopped when the device was withdrawn. Resurfacing implants comprised 10% of all hip replacements between 2004 and 2007, but accounted for less than 2.5% of the total in 2011.

Impact on health: There are circa 93,000 patients with ASR implants worldwide whose health had been impacted since 2010. Considerable numbers of people have had their circulating blood metal ions levels measured, and as a result the National Joint Registry for England and Wales 9th Annual Report (2012) states that revision rates (removal and replacement of the implant by another type of articulation) for the ASR implant after 7 years *in situ* was 24.22% of all patients. Measurement of blood metal ions is now an accepted part of monitoring MOM implants in situ world-wide. Had this release of metal ions from MOM hip implants gone undetected, the toxicological and health consequences for the increasing number of patients receiving these implants worldwide would have continued to increase.

Impact on NHS practice and procedures: Professor Grant was a member of the expert group 'Biological Effects of Wear Debris from Metal-on-Metal Bearing Surfaces' that discussed the

recommended limit of 7 µg/l circulating metal ions levels in the blood of patients with MOM hip implants. Awareness of the risk of metal ion release from metallic implants was highlighted by the Medicines and Healthcare Products Regulatory Agency (MHRA), and in April 2010 an initial Medical Device Alert was released. This was followed in September 2010 with an immediate action notice to medical directors, orthopaedic surgeons and staff involved in the management of patients with joint replacement implants. Specific instructions given at that time were "*Do not implant DePuy ASR hip replacements. Return all unused ASR hip replacement implants to the manufacturer. Inform all patients implanted with ASR hip replacements about this recall and schedule them for a follow-up visit*." [Source F]

Impact on manufacture of joint replacements: The MHRA Medical Device Alerts brought the health risks of metallosis to the attention of manufacturers, and the trend has moved significantly away from the use of metal –on-metal hip implants towards alternative articulations.

Economic impact: Many patients worldwide are now suing DePuy; the research findings from the Strathclyde project have been used as evidence in a number of these cases in Scotland. By the end of July 2013 more than 11,000 cases against DePuy are pending in US law courts alone, and the first compensation case in USA was settled in March 2013 with award of 8.3 million US Dollars [Source G]

5. Sources to corroborate the impact (indicative maximum of 10 references)

A. Vice President Research & Development, DePuy International, can be contacted to support the claim that he brought the leaching of metal ions from metal orthopaedic implants to Grant's attention in 2006, and initiated the funding of the research

B. Orthopaedic surgeon, Southern General Hospital, can be contacted to support the claim that the researchers at Strathclyde measured metal ion levels and determined lymphocyte numbers in blood samples from patients with MOM implants.

C. Senior Engineering Fellow (Hips) at DePuy International Ltd, Leeds, can be contacted to support the claim that he acted as Industrial supervisor to Moeed Akbar and had direct first hand access to all the data generated during the research from 2007-2011.

D. Chairwoman of MHRA Expert Group on the Biological Effects of Wear Debris from Metal-on-Metal Bearing Surfaces can be contacted to support the claim that MHG was a member of the expert group that discussed the recommended limit of 7ppb circulating metal ions levels for patients with MOM hip implants prior to release of the initial MDA in April 2010.

E. Voluntary withdrawal notice issued by DePuy on 24 August 2010 taking the ASR device off the market immediately
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/fieldsafetynotices/FieldSafetyNoticesformedicaldevices/CON076186

F. MHRA Medical Device Alert (MDA) withdrawing the ASR™ implant from the market.
http://www.mhra.gov.uk/home/groups/dts-bs/documents/medicaldevicealert/con093791.pdf Ref: MDA/2010/069 Issued: 07 September 2010 at 13:00. Device:DePuy ASR™ hip replacement implants.

G. http://mdd.blogs.medicaldevicedaily.com/2013/03/13/gigantic-jury-award-in-first-jj-hip-implant-case-is-breathtaking-as-an-initial-benchmark/?elq=08089bca63f94f748f506befdd2bb2e6&elqCampaignId=5241
This is the first insurance claim settled with a patient in USA receiving 8.3 million USD.