Institution: University of Strathclyde		
Unit of Assessment: B12 - Engineering		
Title of case study: Research on metal-on-metal hip resurfacing implants leads to global withdrawal of implants, with economic and health benefits for patients worldwide		
Period when the underpinning research was undertaken: 2006-2012		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Prof Helen Grant	**Role(s) (e.g. job title):** Professor	**Period(s) employed by submitting HEI:** 01/10/1988 – present
Period when the claimed impact occurred: August 2013 – July 2020		
Is this case study continued from a case study submitted in 2014? Yes		

1. Summary of the impact

Research by Professor Grant directly contributed to the Medicines and Healthcare Products Regulatory Agency's (MHRA) medical device alert and subsequent product recall in 2010 for many DePuy metal-on-metal hip replacement and resurfacing implants. Since August 2013, the company has faced lawsuits in USA, Canada, UK, Ireland, Australia and India, with over GBP4,500,000,000 of compensation awarded so far. Withdrawal of other manufacturer's metal-on-metal implants followed from 2015 onwards, with these companies also facing substantial claims for compensation. Updated MHRA guidelines in 2017, with input from Grant, highlighted the need to monitor Cobalt and Chromium in blood of patients who had undergone hip replacement. The medical profession and the wider public have become increasingly aware of the risks of raised levels of cobalt and chromium, and designs have improved as a result.

2. Underpinning research

The ASR™ (Articular Surface Replacement) system was a hip resurfacing implant made by DePuy International Ltd, part of the multi-national Johnson & Johnson group of companies. This metal-on-metal (MoM) hip was made of cobalt chrome alloy and was developed and marketed as an option for younger or more active arthritic patients as it was believed that the reconstruction might be more durable and less prone to dislocation. However, it had a higher than expected failure rate, causing pain, swelling around the hip, and deteriorating hip function due to release of metal ions cobalt (Co) and chromium (Cr), locally, and into patients' blood circulation. Grant's research on metal-induced toxicity came to the attention of then Global Head of Research & Development, DePuy International, during a visit to Strathclyde University in 2006. They highlighted the leaching of Cr and Co ions from metal orthopaedic implants to Grant and arranged PhD sponsorship to initiate further investigations. Researchers at Strathclyde worked closely with Mr Dominic Meek, consultant orthopaedic surgeon, then based at Southern General hospital, Glasgow, who provided access to patient samples, and advised on all clinical aspects of the work.

In-vitro research demonstrated that high concentrations of Cr and Co ions were toxic to human lymphocytes, leading to apoptosis – changes in the cell structure causing cell death [**R1**]. Even at lower concentration levels, exposure to metal ions could affect events at a molecular level, thereby impeding lymphocyte proliferation and contributing to altered immune system function in patients with Co-Cr implants [**R1**]. Chronic exposure to Cr at concentrations measured in the blood of patients with MoM orthopaedic implants also caused toxicity to both osteoblasts and monocytes in-vitro [**R2**]. Cr levels were measured in a pseudo-tumour and data published in the US Journal of Bone & Joint Surgery [**R3**]. The research into the distribution of Cr in patients' blood showed that circulating metal ion levels should be measured in whole blood, rather than in plasma/serum, as Cr was mainly partitioned in red blood cells [**R4**].

In-vivo research demonstrated that ASR™ wear debris implanted into mice caused a local inflammatory reaction, and strong recruitment of macrophages/monocytes, granuloma and fibrosis [**R5**]. Expression of inflammatory genes was induced, and Cr and Co ions were released into the animals' blood. Co was a mobile ion, found in liver, heart, brain, testes, kidney and spleen [**R6**]. Released Cr was not disseminated significantly through the body [**R6**]. Two unpublished clinical studies by the same research team, funded by DePuy, found that 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. 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.

3. References to the research (Strathclyde affiliated authors in **bold**)

R1 **Akbar M**, Brewer J, **Grant MH**. The effect of chromium and cobalt ions on primary human lymphocytes in-vitro. *Journal of Immunotoxicology*, 2011; 8(2), 140-149. https://doi.org/10.3109/1547691x.2011.553845

R2 **Raghunathan VK**, **Tettey JNA**, **Ellis E** and **Grant MH**. Comparative chronic in-vitro toxicity of hexavalent chromium to osteoblasts and monocytes. *Journal of Biomedical Materials Research*. 2009, 88, 543-550. https://doi.org/10.1002/jbm.a.31893

R3 Clayton RAE, Beggs I, Salter D, **Grant MH**, Patton JT and Porter DE. Inflammatory pseudotumour associated with femoral nerve palsy following MoM resurfacing of the hip: A case report. *Journal of Bone and Joint Surgery*. 2008, 90 (9), 1988-1993. (Available on request from HEI)

R4 **Afolaranmi GA**, **Tettey J**, Murray H, Meek RMD, **Grant MH**. The effect of anticoagulants on the distribution of chromium VI in blood fractions. *Journal of Arthroplasty*. 2010; 25, 118-120. https://doi.org/10.1016/j.arth.2008.10.012

R5 **Akbar M**, Fraser AR, Graham GJ, Brewer J, **Grant MH**. Acute Inflammatory response to cobalt chromium orthopaedic wear debris in a rodent air-pouch model. *Journal of the. Royal Society Interface.* 2012; 9 (74) 2109-19. https://dx.doi.org/10.1098%2Frsif.2012.0006 [REF2 in 2014]

R6 **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. *Journal of Biomedical Materials Research*. 2012; 100(6), 1529-38. https://doi.org/10.1002/jbm.a.34091

Notes on the quality of research: This body of research has been the subject of rigorous peer review ahead of publication. The research was funded directly by the implant manufacturer based on the researchers' expertise (e.g. Grant, MH. Measurement of circulation trace metal levels. DePuy International Ltd., 01/01/2009-30/04/2011, GBP194,909). The work has been widely published and presented at conferences, both as peer-reviewed communications and invited talks. The research findings influenced the design of many parallel studies worldwide (e.g. Devoy et al., 2016, DOI: 10.1016/j.toxlet.2016.05.008) and **R3** raised awareness of Co-Cr implants risks to clinicians (e.g. Campbell et al., 2010, DOI: 10.1007/s11999-010-1372-y).

4. Details of the impact

The underpinning research was a significant part of a body of research in the UK and elsewhere that was a precursor to the withdrawal of the DePuy ASR implant. The Strathclyde team was the first group to show dissemination of metal ions from ASR wear debris in an animal model, and the first to demonstrate the mobility of cobalt ions in-vivo and their clear uptake into organs [**S1**]. Grant was a member of the Medicines and Healthcare Products Regulatory Agency (MHRA) Expert Group on the Biological Safety of Metal Orthopaedic implants (2006- 2010), and in April 2010 an initial Medical Device Alert was released by the MHRA. Strathclyde research was also directly disseminated to DePuy at regular six-monthly meetings from 2007 to 2011, and influenced the decision to eventually recall their ASR hip replacement and resurfacing systems in August 2010 and discontinue their Pinnacle metal-on-metal (MoM) implants in March 2013 [**S1**]. Since August 2013, the Strathclyde research and subsequent recall of DePuy MoM hip replacement and resurfacing systems has resulted in:

- **Informed compensation claims against Johnson & Johnson/DePuy**, leading to economic benefits for claimants and greater accountability for the Johnson & Johnson/DePuy brand.
- **Updated MHRA guidelines and raised awareness among medical professionals** of Co and Cr toxicity following MoM hip replacement, leading to more effective monitoring and care of patients with MoM hip implants.
- **Improved hip replacement options for patients**, through withdrawal of other MoM replacement hip joints and changes to hip replacement materials and design.

Informed compensation claims against Johnson & Johnson/DePuy

Following the recall of DePuy MoM hip replacement and resurfacing systems in August 2010, lawyers began contacting Prof Grant and Mr Meek for information on blood metal ions to support claims from patients and the NHS [**S1**]. Since August 2013, the company has faced lawsuits worldwide, including USA, UK, Australia, Canada, India and Ireland, with an estimated GBP4,597,800,000 paid in settlements and jury verdicts so far [**S2**].

USA: In November 2013, DePuy announced that the company and lawyers representing ASR hip plaintiffs had reached a GBP1,569,750,000 deal to compensate patients. Under this settlement claimants were to receive a base award of GBP156,975, subject to reductions. This base award could go higher for patients who could demonstrate '***extraordinary injuries'***. This also did not bar compensation for patients whose hips might fail in the future, which could add billions to the value of the final settlement [**S3a**]. In 2019 Johnson & Johnson set aside an additional GBP788,000,000 to settle up to 6,000 lawsuits filed by patients who needed to have Pinnacle implants removed [**S3b**].

United Kingdom: In 2015, DePuy set up the ASR reimbursement programme to cover the costs of tests and treatment for those whose hip replacement systems have been involved in the recall, especially those who had to undergo additional surgery to repair damages caused by the recalled device. DePuy offered to pay treatment costs, out-of-pocket expenses, lost wages and travel costs. A spokesperson for DePuy confirmed they had '*provided reimbursement to the NHS trusts and other healthcare providers for applicable testing and treatment, including expenses related to revision surgeries.*' [**S3c**]. It is estimated that the cost of annual follow up with patients in line with the MHRA guidance is GBP8,264,064 [**S4**].

Australia: In March 2016, the Australian Federal Court approved a settlement of GBP133,475,000, without admission of liability by DePuy or Johnson & Johnson. It is estimated that approximately 1,700 claimants will be eligible to share in the settlement, resulting in an average of GBP78,500 each [**S3d**].

Canada: In May 2018, a class action lawsuit was filed in the Supreme Court of British Columbia. Claimants included anyone resident in Canada, with surgical implantation of the ASR™ XL Acetabular Hip System or ASR™ Hip Resurfacing System and with the surgery occurring in Canada. DePuy, while not admitting liability, agreed to a class action for settlement purposes. Eligible claimants could receive up to GBP58,000 if they have undergone a single revision or up to GBP70,000 for a bilateral revision. Those who experienced additional complications, including extraordinary income loss, may receive additional funds up to GBP23,350 [**S3e**].

India: In September 2018, Reuters news agency reported that an Indian government panel had required Johnson & Johnson to pay at least GBP22,400 in compensation to each patient with a faulty ASR hip implant. The panel indicated that there were 4,700 people with ASR implants in India. DePuy had already paid GBP1,535,000 for repeat surgeries and about GBP191,875 in related diagnostic costs in India before the compensation scheme was enforced [**S3f**].

Ireland: An Alternative Dispute Resolution was put in place in December 2015 to deal with the 1,112 cases against Johnson & Johnson lodged with the High Court in Ireland since the withdrawal of the ASR hip replacement system. By January 2019 there were 102 cases remaining in the dispute resolution process. The average award was thought to be in the region of GBP87,570 per claimant [**S3g**].

In addition to the compensation claims, in January 2019, Johnson & Johnson agreed to pay GBP94,212,000 to resolve deceptive marketing claims over the company's MoM hip implants. Attorneys general of 46 U.S. states alleged DePuy had engaged in unfair and deceptive practices in the promotion of its hip implant devices, and had made misleading claims about their longevity, with patients frequently having to undergo a revision surgery before the company's advertised timeframe of five years. Johnson & Johnson, the world's largest maker of health-care products, reported expected growth to slow or halt in 2019, due to a variety of economic factors [**S5**]. One of these factors was a reported GBP1,012,779,000 in litigation expenses before taxes in the fourth quarter of 2018, including litigation around other products. Most of this cost involved claims by patients with hip implants; '*The significant majority of these reported expenses reflect the*

company's efforts to resolve some of the older cases in our medical device business' said a spokesman for the company [**S5**].

Updated MHRA guidelines and raised awareness among medical professionals

Through continued collaboration with Mr Meek and other clinicians, Grant's expertise has influenced further updates to MHRA guidelines on the clinical follow up of patients with MoM hip replacements [**S1**]. Mr Meek attended MHRA meetings in 2015-16 to supply expert advice, based on the underpinning research, to inform medical device alerts for hip implants, which were published in 2015 and updated in June 2017. This guidance now includes advice to monitor cobalt or chromium blood levels and to look for rising blood metal levels, which may indicate potential for soft tissue reaction [**S6**]. Since 2017, medics are also advised that '*after revision surgery, whole blood metal levels of chromium and/or cobalt are expected to fall and symptoms to improve. Persistent symptoms should be investigated for potential causes that include failure of fixation, component loosening, infection and instability. If no cause is found, further blood metal level measurement and cross-sectional imaging should be considered*' [**S6**]. Since the research, and with the publicity surrounding compensation claims, there is now much more rigorous UK wide monitoring of metal ions in the blood following hip replacements [**S1**]. For example, Mr Meek maintains a database (supported by funding from DePuy) for all Greater Glasgow & Clyde patients with MoM bearings. Patients have annual Co and Cr levels checks and any symptoms will trigger cross-sectional imaging of the appropriate joint arthroplasty and repeat testing of blood Co and Cr ion levels [**S1**].

The focus on the health issues of patients following hip implants, and the subsequent series of withdrawals of MoM implants, has contributed to raised awareness across the medical profession of the toxic effects of cobalt and chromium ions at the site of an implant, and in particular Grant's research on the mobility of cobalt ions once in the bloodstream. Medical practitioners and researchers are now reporting a wide range of other symptoms. This includes a paper by a consultant psychiatrist in 2016 [**S7**] reporting *'the first case series suggestive of clinically significant depressed mood and neurocognitive impairment following MoM hip failure with concomitant chromium and cobalt toxicity.*' This paper cites Grant's research, and recommends that '*all clinicians, including those working the fields of orthopaedic, psychiatry and primary care should be aware of the need to assess the neuropsychiatric state of their patients after MoM implant operation'*, and also that '*patients presenting with neuropsychiatric symptoms de novo and who have had orthopaedic implant surgery, should have investigations for chrome and cobalt toxicity*.' [**S7**]

Improved hip replacement options for patients

As a consequence of publicity surrounding Johnson & Johnson/DePuy products, and as more data showed the high level of follow-up surgery needed by patients, other manufacturers withdrew a range of metal on metal hip implants. In 2015, Smith & Nephew advised that its Birmingham Hip Replacement system should not be used in patients needing the smaller-sized implants and withdrew components sized 46 mm and smaller from the market [**S8a**]. In June 2015, the US FDA issued a class I recall for the Zimmer M/L Taper with Kinectiv Technology [**S8b**]. In February 2015, the Australian Department of Health required Biomet to issue a Hazard Alert, warning patients that Biomet's MoM M2a hip replacements had a higher than expected rate of failure, and that Biomet had agreed to stop selling these devices [**S8c**]. Several medical device manufacturers, aside from DePuy, have been sued because of health complications allegedly caused by their MoM hip replacement devices, including Biomet, Smith & Nephew, Stryker, Wright Medical, and Zimmer. Combined, these companies have accrued nearly 30,000 lawsuits and paid over GBP2,298,900,000 in settlement pay-outs since January 2014 [**S2**].

With increased life span in many countries, global demand for safe and long lasting hip implants will remain high. From 2017-2018, Grant was the Bioengineering specialist in the development of a European Committee of Standardisation (CEN) method to evaluate the biological impact of wear particles from joint replacements [**S9**]. The output, a CEN Workshop Agreement:

> *'is for use by manufacturers of joint replacements evaluating new and existing materials and designs for human joint replacements and related devices, commercial, industrial and academic laboratories undertaking evaluation of, and studies into, device and material performance, and might be of use to other*

organizations, including regulators, concerned with the potential impact on the health and well-being of recipients of joint replacements.' [**S9**]

As part of this, the group produced a detailed and technical toolkit for the evaluation of the biological impact of metal and ceramic wear particles, which is used widely within the academic, medical and industry sectors [**S9**].

In summary, Strathclyde research demonstrating the dissemination of metal ions from ASR wear debris in an animal model, the mobility of cobalt ions in-vivo and their clear uptake into organs contributed to the 2010 Medicines and Healthcare Products Regulatory Agency's (MHRA) medical device alert and to the subsequent product recall for many DePuy metal-on-metal hip replacement and resurfacing implants. Since 2013, this research, the device alert and the recall have been used to ensure compensation for patients worldwide who have suffered injuries and had to undergo additional surgeries as a result of these implants. The research has also been used to inform updated MHRA guidelines on the clinical follow-up of patients with MoM implants and has raised awareness across the medical profession of the toxic effects of cobalt and chromium ions. Finally, the publicity and increased awareness has resulted in the withdrawal of other MoM implants from market and informed the design and materials of new hip implants.

5. Sources to corroborate the impact

S1 Supporting statement from Consultant Othopaedic Surgeon, Queen Elizabeth University Hospital, dated 14 November 2020.

S2 Drugwatch. Hip Replacement Lawsuits. 07/10/2020. https://bit.ly/2HNWTLy

S3 Collated news articles on compensation claims against Johnson & Johnson/DePuy.

a. Orthopedics. *It's Official – DePuy Settles Hip Lawsuits for $2.5 Billion*. 21/11/2018. https://bit.ly/34JdAk6
b. Lawyers and Settlements. *Johnson & Johnson Resolves Hip Implant Lawsuit for $1 Billion Dollars.* 03/06/2019. https://bit.ly/3jH8yJ3
c. The Guardian. *Firm Pays Out to NHS Over Defective Hip Replacements.* 26/11/2018. https://bit.ly/31TlDsr
d. ABC News. *Class action over defective DePuy ASR hip replacements settles for $250 million*. 31/03/2016. https://ab.co/3mDhl0A
e. Notice of Hearing on Class Certification and Settlement Approval. https://bit.ly/3oDL9vD
f. Reuters. *J&J to Work With India On Compensation For Recalled Hip Implants*. 07/09/2018. https://reut.rs/35RPT8i
g. Irish Times. *Court due to hear six cases against artificial hip maker.* 04/01/2019. https://bit.ly/34EuJeG

S4 Matharu, GS, Mellon, SJ, Murray, DW, Pandit, HG (2015). Follow-Up of Metal-on-Metal Hip Arthroplasty Patients Is Currently Not Evidence Based or Cost Effective. *Journal of Arthroplasty, 30,* 1317-1323.

S5 The Wall Street Journal. *Johnson & Johnson Expects Sales Growth to Slow*. 22/01/2019. https://on.wsj.com/3jHgha6

S6 Medicines and Healthcare products and Regulatory Agency, Medical Device Alerts relating to MoM hip implants, 2015 and 2017 update.

S7 Green, B, Griffiths, E, Almond, S. Neuropsychiatric symptoms following MoM implant failure with cobalt and chromium toxicity. BMC Psychiatry, 2017, 17.

S8 Collated press releases relating to compensation claims against other manufacturers and withdrawal of other MoM implants.

a. Smith & Nephew. *Statement regarding BHR System*. 04/06/2015. https://bit.ly/3jJzBTS
b. US Food and Drug Administration. *Class 1 Device Recall Zimmer M/L Taper Hip Prosthesis with Kinectiv Technology*. 08/06/2015. https://bit.ly/2HS9hKm
c. Australian Government Department of Health. *Biomet M2a metal-on-metal total hip replacement implants.* 09/02/2015. https://bit.ly/34HdcCw

S9 CEN Workshop Agreement 17253-2. Published March 2018.