

<p>Institution: University College London</p>
<p>Unit of Assessment: 15 – General Engineering</p>
<p>Title of case study: Changes to health policy and medical device regulation following analysis of metal-on-metal hip replacements</p>
<p>1. Summary of the impact UCL research into metal-on-metal (MOM) hip replacements has developed evidence affecting the 1.5 million patients with MOM hips worldwide and led, indirectly, to a change in the regulation of all medical devices by the US Food and Drug Administration and the UK Medicines and Healthcare Products Regulatory Agency (MHRA). Direct impacts include stimulation of the first global retrieval programme for medical implants, [text removed for publication], and the development of a change in the MHRA protocol used to monitor all UK MOM hip patients. These have led to improvements in the quality of patients' lives after redo surgery, and supported litigation cases worth billions of dollars against health providers – including Johnson & Johnson – to fund compensation and earlier-than-expected redo hip operations. Public awareness of issues with MOM hips has been stimulated through widespread media coverage and creation of information resources by charities and regulatory bodies.</p> <p>2. Underpinning research In 2004 orthopaedic surgeons John Skinner and Alister Hart used inductively coupled plasma mass spectrometry (ICP-MS) to demonstrate that some of their patients with metal-on-metal (MOM) hip implants released detectable levels of cobalt and chromium in the blood and that this affected circulating immune cells. In 2007, using high-resolution x-ray analysis at the then newly opened Diamond Light Source synchrotron facility, they were able to show for the first time that the corrosion products in human tissue surrounding MOM hips were chromium (III) phosphate rather than any chromium (VI) cancer-causing species, solving a 30-year debate over the chemical speciation of metal debris from hip replacements [5]. The latest finding from their synchrotron work in 2012 showed that cobalt is the likely culprit for the adverse tissue response, even though the predominant metal left behind in the tissues is chromium.</p> <p>In 2006, Skinner and Hart had noted that unexplained pain in a group of patients with MOM hips had required revision surgery to remove and replace the original implants. This type of surgery can be very challenging because of the tissues destroyed by the inflammatory reaction to the cobalt and chromium previously released from the hips. To better understand the mechanism of failure of MOM hip replacements, they devised a programme of international inter-disciplinary research to untangle the complicated relationship between three dimensional (3D) surgical positioning, implant design and patient factors in the performance of hip implants. Implant retrieval analyses provide important insights into the <i>in situ</i> performance of orthopaedic devices and provide critical clues into mechanisms of failure and success. In 2008, they therefore created a consortium of nine orthopaedic manufacturers (all of whom signed a research contract with no restrictions on publication) to fund their foundation of the London Implant Retrieval Centre (LIRC), set up to collect and analyse failed (retrieved) implants from around the world. Since then, they have analysed 1,000 hips, using sophisticated metrology (coordinate measurement and roundness machines) to measure the small amounts of volumetric loss that lead to metal nanoparticle release and consequently, to the presence in the blood of metal ions that cause inflammation of tissues and destruction of muscle, and ultimately require revision of hips [1]. Their use of 3D CT with metal artefact reduction to quantify the effect of surgical positioning on blood metal ion levels, led to their publication of the first study to quantify the effect of all angles of orientation of the cup component [4]. This work was conducted in collaboration with medical statistician Dr Fabiana Gordon at Imperial College. In 2009, the researchers returned to their previous use of ICP-MS to assess the diagnostic test characteristics of blood metal ions for predicting failure. This work, with two groups of patients (well and poor functioning) found a 90% specificity for detecting failure when using a cut-off level of 7 parts per billion. [3]</p> <p>Since 2011, the research has focused on an examination of microscopic wear and corrosion at the tapered junction between head and stem parts of MOM implants [7]. Electrochemical static and dynamic corrosion tests performed under loaded and non-loaded conditions found that surface area and surface finish are important factors in wear and corrosion at interfaces in modular MoM hips. This indicates that the design of the taper junction connecting the head to the stem of the implant can lead to increased metal release. [6]</p>

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In 2011, Skinner and Hart worked with MRI physicist Dr Donald McRobbie at Imperial Healthcare NHS Trust to develop new metal artefact reduction sequence (MARS) MRI protocols that alter the radiofrequency fields to minimise heating and metal artefact around hip implants [2]. The application in patients of these protocols, which won the 2010 Radiological Society of North America Education Exhibit Prize, enabled them to more easily detect soft tissue inflammation and muscle damage adjacent to metal implants [2]. Further work with material science collaborators enabled very sophisticated nano-scale imaging to take a “snapshot” of the corrosion of the metal debris inside cells. This showed both the physical (size, shape and density) and chemical (ionic state / valency) form of the metal debris – the first report of this technique applied to human tissue. [7]

Research conducted between 2008 and 2010 found that, in 50% of patients with implant failures, the levels of material loss were in fact low. This research was the first to emphasise the significance of unexplained patient factors, rather than implant design and surgical positioning, in the failure of MOM hip implants. These patient factors remain the focus of Skinner and Hart’s current research.

The research was conducted in collaboration between UCL and Imperial College London. Alister Hart is currently Professor of Orthopaedic surgery at UCL. The research began in 2004, when he was a clinical lecturer at UCL. Between 2006 and 2012 he was at Imperial College. John Skinner has been a clinical senior lecturer at UCL Institute of Orthopaedics, at the affiliated Royal National Orthopaedic Hospital since 2000. In 2012, Hart returned to UCL and since then the research has been solely conducted at UCL.

3. References to the research

References [1], [3] and [4] best demonstrate the quality of the research.

1. Hart AJ, Muirhead-Allwood S, Porter M, Matthies A, Ilo K, Maggiore P, Cann P, Underwood R, Cobb J, Skinner J. Which Factors Determine the Wear Rate of Large-Diameter Metal-on-Metal Hip Replacements?: Multivariate Analysis of Two Hundred and Seventy-six Components. *J Bone Joint Surg Am.* 2013;95(8):678-85. doi.org/phk
2. Hart AJ, Satchithananda K, Liddle AD, Sabah SA, McRobbie D, Henckel J, Cobb JP, Skinner JA, Mitchell AW. Pseudotumors in association with well-functioning metal-on-metal hip prostheses: a case-control study using three-dimensional computed tomography and magnetic resonance imaging. *J Bone Joint Surg Am.* 2012 Feb 15;94(4):317-25. doi.org/phm
3. Hart AJ, Sabah S, Henckel J, Lewis A, Cobb J, Sampson B, Mitchell A, Skinner JA, The painful metal-on-metal hip resurfacing, *J Bone Joint Surg Br.* 2009 Jun;91(6):738-44. doi.org/dv5qv7
4. Hart AJ, Skinner JA, Henckel J, Sampson B, Gordon F. Insufficient acetabular version increases blood metal ion levels after metal-on-metal hip resurfacing. *Clin Orthop Relat Res.* 2011 Sep;469(9):2590-7. doi.org/bzd7q7
5. Hart AJ, Quinn PD, Sampson B, Sandison A, Atkinson KD, Skinner JA, Powell JJ, Mosselmans JF. The chemical form of metallic debris in tissues surrounding metal-on-metal hips with unexplained failure. *Acta Biomater.* 2010 Nov;6(11):4439-46. doi.org/cw488r
6. Panagiotidou, A., Meswania, J., Hua, J., Muirhead-Allwood, S., Hart, A. and Blunn, G., Enhanced wear and corrosion in modular tapers in total hip replacement is associated with the contact area and surface topography. *J. Orthop. Res.* 2013 Dec;31(12):2032-29. doi.org/phn
7. Matthies, A. K.; Racasan, R.; Bills, P.; Blunt, L.; Cro, S.; Panagiotidou, A.; Blunn, G.; Skinner, J.; and Hart, A. J.: Material loss at the taper junction of retrieved large head metal-on-metal total hip replacements. *J Orthop Res*, 2013 Nov;31(11):1677-85. doi.org/phq

4. Details of the impact

The research described above has directly affected UK and US health policy, industry, clinical practice and patient health.

Changes to international health policy: The identification that a level of 7 parts per billion (ppb) was an important cut-off in the blood levels of metal ions between poor and well functioning hips [4] has informed clinical guidance disseminated around the world and is currently used to monitor all MOM patients across the UK. In 2010, the finding was adopted by the UK health regulator, the MHRA, and incorporated into their guidance on the clinical management of patients with MOM hips as the “action level” above which they recommend further intervention. These guidelines, which were the first in the world to specify how to monitor and treat patients with MOM hips, were disseminated globally in 2010. The “action level” has remained unchanged as of late 2013, and is

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used to monitor 90,000 patients with MOM hips in the UK [a]. John Skinner chaired the MHRA's expert advisory panel looking at soft tissue reactions associated with MOM hip replacements. The panel's report was disseminated among patients, GPs and surgeons as well as industry and healthcare providers. [b] NICE (the National Institute for Health and Care Excellence) updated its recommendations for hip replacement surgery in October 2013, issuing stricter guidelines that rule out the use of most types of MOM implant in the UK.

The research has also indirectly resulted in a change in the regulation of all metal-on-metal hip devices in the United States and United Kingdom. In the US, the problems with MOM hips, including that identified by the research above, led to a technology overview undertaken by the American Academy of Orthopaedic Surgeons (AAOS) in 2011 [c]. This led to an FDA order, in January 2013, requiring manufacturers of MOM total hip replacement systems to submit premarket approval applications, citing reports including the MHRA expert advisory panel report [d]. In the United Kingdom, the MHRA and British Orthopaedic Association have gone further in setting up the "Beyond Compliance" initiative in May 2013. This initiative is intended to improve the rigour of CE marking processes before an implant is sold, and to provide high-quality surveillance and a decision-making process to identify failures at the earliest point and suggest appropriate action. [e]

Development of new and revised clinical guidance in the UK and abroad: International health regulatory agencies and professional bodies (including the FDA and Australian Therapeutic Goods Association [f], American Association of Orthopaedic Surgeons [g], British Hip Society, Arthritis Research UK) have used the research described above to create their own recommendations for the 1.5 million patients worldwide that have MOM hips. In particular, the research team's long-running analysis of the mechanism of hip failure has been widely welcomed by, and influential among, surgeons. Regulatory bodies including the FDA have produced advice for surgeons based on the research, particularly the investigations (metal ion testing and soft tissue imaging) first identified in output [3] [h]. According to Dr J Jacobs, president of the American Academy of Orthopaedic Surgeons, output [1], above "is an important contribution to our understanding of the performance of the current generation of large femoral head metal-on-metal devices." He added: "it is informative for the surgeon regarding component positioning." [i]

Changes to clinical practice and subsequent cost savings: The sensitivity and specificity analysis of blood metal ions and the MARS MRI interpretation enabled the MHRA to create clinically usable clinical management guidelines, as shown by their adoption across the NHS [j]. As a result, blood metal ion testing and MARS MRI, which were unavailable in all NHS hospitals in 2006, are now routinely available, and have revolutionised the management of patients with metal-producing hips, most of which are metal-on-metal but now also include those with junctions between two different types of metal. The MARS MRI protocols have supported more effective clinical management, by reducing either unnecessary revision procedures or delays to revision procedures to prevent irreversible muscle damage. The reduction in unnecessary revision procedures alone produces very significant NHS cost savings, since each surgery costs more than £10,000. Reducing delays to revision procedures likewise supports the reduction of productivity losses, not just for the NHS and the UK economy more broadly, but also for individual patients.

Subsequent impacts on patient health and wellbeing: A crucial result of the work has been to improve the quality of life of patients suffering from painful hip replacements. Patients who experience an adverse reaction to a MOM hip now have them replaced with a ceramic-on-ceramic or ceramic-on-polyethylene implant and the level of metal ions in the patient's blood slowly falls; after 50 days, the levels are reduced by half [k]. Moreover, by identifying some of the factors that can predict if a patient will have problems with a MOM hip, such as hip size, and the patient's age and sex, the research has led to a reduction in the number of patients receiving these hips and thus being at risk of complications. The National Joint Registry (NJR) monitors all joint replacement operations in the UK. Their latest report notes that MOM stemmed hip replacement and hip resurfacing have virtually ceased, with fewer than one in one thousand hip replacements performed in 2012 being of this type [l], having peaked in the UK in 2008 at around 8,000 operations. The research received widespread media coverage, helping alert patients to potential problems and symptoms; coverage included features on Newsnight, the BBC website and in national newspapers including the Daily Telegraph, Daily Mail and Guardian [m].

Accountability within industry: The LIRC is the first truly global (22 countries, all continents)

retrieval programme for medical implants: removing 4,700 components from 2,300 patients since 2008. Industry, patients and surgeons regularly approach the researchers to provide independent reports. In August 2010, Johnson & Johnson subsidiary DePuy issued a global recall for two of its hip replacements after NJR data showed higher than expected revision rates. [text removed for publication]. In May 2013, Johnson & Johnson announced it was phasing out production of all its MOM hips [o].

Evidence from the research has been used to support patient claims against the manufacturers of these faulty implants, including one claim leading to an \$8 million pay out to a patient with the DePuy implant. A number of other manufacturers have also recalled hips. Johnson & Johnson have allocated more than \$1 billion, and other health providers many more billions of dollars, to pay for earlier-than-expected redo hip operations [p]. The recent work on the taper connection [7] is informing manufacturers about the best designs to use, and guiding their implant testing and assessment [q].

Increased public awareness: Charities, regulatory agencies and professional bodies have used the research to create **information resources for the public and patients**. For example, Arthritis Research UK's online clinical advice [r], based on the research, is viewed more than 1,000 a month [s]. ARUK's web statistics show that users stay on the page for approximately five times longer than the site average, demonstrating that people are engaging with the content [s].

5. Sources to corroborate the impact

- [a] 7ppb cut off in: MHRA Medical device alert MDA/2012/036, 25 June 2012. This MDA replaced advice previously given, from 2010, in MDA/2010/033, MDA/2010/069 and MDA/2012/008. <http://bit.ly/GzzCYA>
- [b] For Skinner's chairmanship of the MHRA expert advisory group, and references to the research above, including output [3], see pp 1, 13, 14 (refs 10,14,40): <http://bit.ly/1aGYKWL>
- [c] "Modern metal-on-metal hip implants, a technology overview", AAOS, 2011. The research above, including outputs 3 and 4, is referenced on pp 72-73 [refs 9, 10, 14 (of 24 papers reviewed)] http://www.aaos.org/research/overviews/Metal_On_Metal.pdf
- [d] FDA premarket approval order: 1.usa.gov/1fF7rqP; MHRA report cited: 1.usa.gov/17NKvfZ
- [e] Beyond Compliance, set up to address finding of Skinner's MHRA expert panel, that problems were caused by widespread use of devices despite insufficient data: <http://bit.ly/1aP1SxW>
- [f] Recommendations for metal ion testing and soft tissue imaging: US FDA <http://1.usa.gov/16TcAB8>; Australia Therapeutic Goods Administration (and see ref 4 on their list) <http://www.tga.gov.au/hp/information-devices-mom-hip-implants.htm>
- [g] Information statement from AAOS (see ref 9 in their list): <http://bit.ly/1aGYPth>
- [h] FDA advice to surgeons: metal ion testing and soft tissue imaging <http://1.usa.gov/18Ld3ui>
- [i] Commentary by Dr Jacobs on the use of output [1] by surgeons: <http://bit.ly/1aGY115>
- [j] For an example of NHS adoption of the MHRA MARS MRI guidelines, see the Hampshire Hospitals Trust implant follow-up protocol: <http://bit.ly/18bXpUq>
- [k] "Metal hip joints: The facts", Choice Magazine, Aug 2012, details improvements to patients after redo surgery: <http://bit.ly/1ePF2ug>
- [l] NJR confirmation that MOM hip operations have virtually ceased, 10th Annual Report, p.158: <http://bit.ly/1k3kRr>; Fig. 3.3 on p.134 shows the increased risk to patients of MOM hips.
- [m] Newsnight feature: bbc.in/170FvUN; Links to stories in national UK media: bit.ly/18JrBrZ
- [n] [text removed for publication]
- [o] Johnson & Johnson MOM phase out: <http://nyti.ms/15GfvmF>
- [p] Page 7 of Johnson & Johnson 2012 Historical Financial Review confirms \$1 billion losses 2010-2012 claim: <http://bit.ly/1hhsomX>; \$8 million award: <http://nyti.ms/19jluHZ>
- [q] An email from Director of Hip Research at Stryker Orthopaedics confirms that the research is informing manufacturers designs. Available on request.
- [r] Clinical management guidelines for Arthritis Research UK: Metal-on-metal hip replacement Q and A. John Skinner & Alister Hart. <http://bit.ly/1aGZP0y>
- [s] Correspondence from ARUK confirms their website usage information. Available on request.