**Institution:** University of Bristol

**Unit of Assessment:** 1 – Clinical Medicine

**Title of case study:** Substantial changes in worldwide healthcare policy and the practice of joint replacement result from research into the failure rates of and systemic effects of metal-on-metal hip replacements.

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

Research into the field of metal-on-metal (MoM) arthroplasty (joint replacement) conducted at the University of Bristol in conjunction with the National Joint Registry of England and Wales (NJR) has led to a fundamental change in the practice of arthroplasty around the world and in the clinical follow up of patients. High failure rates have been identified nationally in England and Wales for MoM total hip arthroplasty and certain designs of resurfacing arthroplasty in work conducted by our department. Deleterious systemic effects of wear debris produced by these implants have also been identified by our research. The use of these devices has declined from 14% of procedures in 2008 to less than 1% in 2012. Citing our research, national bodies including NICE (2014), the MHRA (2011 & 2012), the UK Department of Health (2012), British Orthopaedic Association (2011 & 2012), NJR (2012), British Hip Society (2011 & 2012) and the US Food and Drug Administration (FDA) (2013) have issued guidance suggesting the restricted use of such devices or close surveillance of patients in whom these devices have been implanted.

2. **Underpinning research** (indicative maximum 500 words)

University of Bristol research concerning MoM arthroplasty has followed three arms: epidemiology (led by Professor Blom), clinical (led by Professor Blom and Dr Case) and basic science (led by Dr Case). Professor Blom is an orthopaedic surgeon and Head of the group, Dr Case is a Consultant Senior Lecturer; both have been employed at the University throughout the period of the REF.

The University’s research into the field began in 1994 when we demonstrated widely-disseminated metal wear particles from patients with hip implants post-mortem in the local tissues, lymphatic system, liver, spleen and brain when compared to controls without implants.[1] This raised the possibility of long-term deleterious effects in these patients from exposure to metals, as has been highlighted by the recent concerns of the regulatory bodies in Europe and the US (European Commission and FDA). Our follow-up study published in 1996 demonstrated an increase in chromosomal aberrations in local soft tissues for patients with implants in situ when compared with those with no implant in situ and clonal lymphocyte expansion in 2/21 of these patients with more than 10 years follow-up.[2] Further studies published between 2001 and 2005 demonstrated increased levels of aneuploidy (three fold) and chromosomal translocations (two-fold) in the peripheral blood lymphocytes of patients with hip implants in situ. The level of damage appeared to be influenced by the alloy used (titanium alloys leading to aneuploidy but no translocations, cobalt-chrome (CoCr) leading to both and stainless steel not leading to either). These effects were observed over periods ranging from two years after implantation of a well-fixed device to 11 years after implantation at revision for a loose device. Wear debris collected from such loose implants were observed to cause the same types of chromosomal aberrations in human cells in tissue culture.[3] Recent studies in 2009, 2010 and 2011 have shown that cobalt chrome nanoparticles can cause chromosome damage in human cells including human embryonic stem cells across a placental cell barrier and can cause DNA damage in a foetus in vivo.[4,5] This raises the possibility of teratogenicity in the baby of a woman with a hip replacement in situ. The work described in the period 2008-2011 has been led by the University of Bristol and conducted in collaboration with a number of units including Professor Ingham at the University of Leeds.

Allied to this basic science approach to researching direct cellular effects of wear debris from total hip replacement, we have studied the epidemiological evidence regarding MoM bearing surfaces in comparison with the alternative bearing surfaces in use. We hold the contract for the analysis of the NJR, the largest joint arthroplasty database in the world. Research on 434,560 primary hip replacements, of which 31,932 were resurfacings, demonstrated that the failure rates of hip replacement were higher for resurfacing than for conventional metal-on-polyethylene (MoP) hip
replacement at five years.[6] Failure rates were much higher in women and in smaller bearing sizes for resurfacing (predicted five-year failure rates for women by head size: 8.3% (95% confidence interval 7.2-9.7) with a 42mm head, 6.1% (5.3-7.0) with a 46mm head and 1.5% (0.8-2.6) with a 28mm MoP hip replacement). In men with resurfacings, higher failure rates were observed with smaller joint heads (4.1% (3.3-4.9) with a 46mm head, 2.6% (2.2-3.1) with a 54mm head and 1.9% (1.5-2.4) with a MoP hip replacement), while rates of failure were similar between larger resurfacings and total hip replacement, only 23% of men had these size implants put in. When total hip replacements with different bearing surfaces were analysed, higher failure rates were observed in larger bearing MoM total hip replacements when compared to the alternatives. Whilst this failure rate increased as head size increased, the opposite pattern was seen in ceramic-on-ceramic total hip replacements.[7] In response to a request from the MHRA, we analysed the risk of developing specific and all cancers after metal hip replacement with MoM bearing surfaces and found no increase in cancers up to 7 years after surgery compared with the general population and alternative bearings.[8]

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


Recent Grants Pertaining to this Work:


blood metal ion level testing to evaluate the function of the joint. They further note that imp
replacement and if any symptoms develop, the
report. The FDA rec
and guidance issued in the UK as well as similar guidance in Canada and Australia is cited in the
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metal wear products from Orthopaedic implants and the risk of the early need for revision in metal
performances in England and Wales,[b] The worldwide trend followed the UK lead in the
use of these implants and the advice given by the Chief Medical Officer directly cited the research
of the University of Bristol.

**Chief Medical Officer guidance**

On the 12 March 2012, in direct response to and quoting our Lancet publication, the Chief Medical
Officer and the Medical Director for NHS England wrote to all Chief Executives of NHS Trusts,
Strategic Health Authorities and independent hospitals advising them on implant choice[a] This
advice, empowered by the research of the University of Bristol, has contributed to a worldwide
decline in the use of metal-on-metal hip replacements and they now make up less than 1% of hip
replacements performed in England and Wales,[b] The worldwide trend followed the UK lead in the
use of these implants and the advice given by the Chief Medical Officer directly cited the research
of the University of Bristol.

**Regulatory Body and Learned Society Advice: UK**

Various bodies in the UK have issued advice regarding the long-term systemic risks of exposure to
metal wear products from Orthopaedic implants and the risk of the early need for revision in metal-
on-metal bearings. Partly as a result of research from the University of Bristol, the MHRA issued
updated advice to surgeons that patients with metal-on-metal hip replacements should be
monitored annually for the life of the hip replacement.[c,d] Similar guidance has been issued by
both the British Hip Society [e] and the British Orthopaedic Association.[f] Accordingly, long-term
annual follow-up, with monitoring of metal ion levels and cross-sectional imaging as dictated by
symptoms and individual patient risk, is now standard practice in the UK. NICE has recently
circulated draft recommendations based on our publications. These recommend against using
metal-on-metal bearings. The definitive guidance is due in 2014.

**European Commission**

The European Commission has asked the Scientific Committee on Emerging and Newly Identified
Health Risks (SCENIHR) to assess the safety of metal-on-metal joint replacements with a
particular focus on hip implants. Dr Case is an expert adviser. In the light of the above
considerations, SCENIHR is requested to provide a scientific opinion on the safety of metal-on-
metal joint replacements with a particular focus on hip implants.[g] The Joint Research Centre
scientific and policy report for the European commission on hip replacements wrote in their
conclusion “Long term effects are still not fully assessed especially in terms of carcinogenicity,
genotoxicity and reproductive toxicity”.[h] They quoted 210 papers, of which six were from the
University of Bristol (the most quoted research group).

**US Food and Drug Administration**

The FDA has issued guidance to patients who have received a metal-on-metal implant. The advice
and guidance issued in the UK as well as similar guidance in Canada and Australia is cited in the
report. The FDA recommend follow-up every 1 to 2 years to check on the status of the hip
replacement and if any symptoms develop, the use of joint aspiration, cross-sectional imaging and
blood metal ion level testing to evaluate the function of the joint. They further note that implants

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[14] National Institute of Health Research Programme Grant. Improving patients' experience and
statistical support and analysis programme. PI: Prof Blom. Dates: 2011-2014. Amount: £0.6m.
may have an effect on general health, including hypersensitivity reactions, cardiomyopathy, neurological and psychological changes, and renal and thyroid function impairment.[i]

Other International Regulatory Bodies
Citing the research from the University of Bristol regarding the risk of cancer following metal-on-metal joint replacement,[8] as well as the guidance issued by the MHRA, the Therapeutic Goods Administration (TGA) of Australia has recommended a follow-up regime for patients with metal-on-metal joint replacements that includes annual or more frequent follow ups, the use of cross sectional imaging as well as plain radiography and the measurement of blood metal ion levels routinely as part of follow-up.[j] The TGA recommends revision surgery if there are any symptoms, imaging abnormalities or where metal ion levels are rising. Health Canada issued guidance in May 2012 advising annual follow-up of patients and the use of cross-sectional imaging and blood metal ion level analysis where there are any symptoms or physical examination abnormalities.[k]

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


[g] Scientific Committee on Emerging and Newly Identified Health Risks Request for a scientific opinion on the safety of metal-on-metal joint replacements with a particular focus on hip implants [Internet]. Brussels: European Commission; 2013 Mar. Available from: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_q_033.pdf


