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)

[1] Case CP, Langkamer VG, James C, Palmer MR, Kemp AJ, Heap PF, et al. Widespread dissemination of metal debris from implants. J Bone Joint Surg Br. 1994 Sep;76(5):701–12. PMID: 8083255

[2] Case CP, Langkamer VG, Howell RT, Webb J, Standen G, Palmer M, et al. Preliminary observations on possible premalignant changes in bone marrow adjacent to worn total hip arthroplasty implants. Clin Orthop Relat Res. 1996 Aug;(329 Suppl):S269–79. PMID: 8769341

[3] Davies AP, Sood A, Lewis AC, Newson R, Learmonth ID, Case CP. Metal-specific differences in levels of DNA damage caused by synovial fluid recovered at revision arthroplasty. J Bone Joint Surg Br. 2005 Oct;87(10):1439–44. PMID: 16189324

[4] Bhabra G, Sood A, Fisher B, Cartwright L, Saunders M, Evans WH, et al. Nanoparticles can cause DNA damage across a cellular barrier. Nat Nanotechnol. 2009 Dec;4(12):876–83. DOI: 10.1038/nnano.2009.313.

[5] Sood A, Salih S, Roh D, Lacharme-Lora L, Parry M, Hardiman B, et al. Signalling of DNA damage and cytokines across cell barriers exposed to nanoparticles depends on barrier thickness. Nat Nanotechnol. 2011 Dec;6(12):824–33. DOI: 10.1038/nnano.2011.188.

[6] Smith AJ, Dieppe PA, Howard PW, Blom AW, National Joint Registry for England and Wales. Failure rates of metal-on-metal hip resurfacings: analysis of data from the National Joint Registry for England and Wales. Lancet. 2012 Nov 17;380(9855):1759–66. DOI: 10.1016/S0140-6736(12)60989-1

[7] Smith AJ, Dieppe PA, Vernon K, Porter M, Blom AW, National Joint Registry of England and Wales. Failure rates of stemmed metal-on-metal hip replacements: analysis of data from the National Joint Registry of England and Wales. Lancet. 2012 Mar 31;379(9822):1199–204. DOI: 10.1016/S0140-6736(12)60353-5

[8] Smith AJ, Dieppe PA, Porter M, Blom AW, National Joint Registry of England and Wales. Risk of cancer in first seven years after metal-on-metal hip replacement compared with other bearings and general population: linkage study between the National Joint Registry of England and Wales and hospital episode statistics. BMJ. 2012;344:e2383. DOI: 10.1136/bmj.e2383

Recent Grants Pertaining to this Work:

[9] Medical Research Council, Research Grant. Biological consequences of exposure to prosthetic nanoparticles. PI: Prof Ingham, University of Leeds; Co-applicant: Dr Case. Dates: 1/6/2008-31/5/2011. Amount: £434,000

[10] Arthritis Research UK Project Grant. Is there systemic genotoxicity after hip replacement using resurfacing arthroplasty? PI: Dr Case. Dates: 08/10/2009 -05/2011. Amount: £100,124

[11] Furlong Foundation. Could physiologically relevant orthopaedic ions cause indirect DNA and chromosome damage to human embryonic stem cells across a trophoblast cell barrier? PI: Dr Case. Dates: 1/1/2011-2014. Amount: £60,000

[12] Medical Research Council, Research Grant. Dissecting mechanisms of nanoparticle-mediated foetal toxicity. PI: Dr Case. Dates: 1/10/2011-1/10/2015. Amount: £82,000

[13] Medical Research Council, Research Grant. Use of nanoparticles to deliver growth signals to the placenta. PI: Dr Case. Dates: 1/1/2013-1/1/2016. Amount: £590,168.68

[14] National Institute of Health Research Programme Grant. Improving patients' experience and outcome of total joint replacement. PI: Prof Blom. Dates: 2008-2011. Amount: £2,059,777
[15] Healthcare Quality Improvement Partnership. Contract to run the National Joint Registry statistical support and analysis programme. PI: Prof Blom. Dates: 2011-2014. Amount: £0.6m.

4. Details of the impact (indicative maximum 750 words)

Annually, over 1 million people worldwide undergo arthroplasty. The use of metal-on-metal bearing surfaces increased rapidly until 2008/2009, when it represented about 35% of hip replacements in the US and 20% of hip replacements in the UK. Research from the University of Bristol first raised concerns about the biological effects of these implants in 1994 and went on to identify potential local and systemic problems culminating in the largest epidemiological studies of these implants ever published, which showed unequivocally that these implants fail at an unacceptably high rate. These two Lancet publications drew the public's as well as the regulatory bodies' attention to the problem, resulting in extensive worldwide media coverage in print, radio and television, including BBC national news, the cover of the Lancet and Radio 4's Today programme. The University of Bristol research has led to the issuing of guidance from a number of sources worldwide regarding the choice of implants for total hip replacement and the follow-up regime of patients with implants at high risk of failure in situ. The dramatic decrease in use of these prostheses, consequent on our work, will save countless patients from unnecessary suffering, complex revision surgery and vast cost in healthcare resources and societal impact.

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

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)

[a] Davies S, Keogh B. Metal on Metal Hip Replacements. Department of Health; 2012 Mar. Major UK Directive citing the research described. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/215116/dh_133035.pdf

[b] NJR Steering Committee. National Joint Registry for England and Wales: 9th Annual Report. njrcentre.org.uk. NJR Steering Committee; 2012. Available from: http://www.njrcentre.org.uk/njrcentre/Reports,PublicationsandMinutes/Annualreports/tabid/86/Default.aspx. Corroborates the major decline in use of metal-on-metal arthroplasty.

[c] MHRA Press Release. mhra.gov.uk. London: Medicines and Healthcare Products Regulatory Agency; 2012. Available from: http://www.mhra.gov.uk/home/groups/comms-po/documents/news/con143785.pdf. MHRA stipulation of need for annual monitoring.

[d] Metal-on-Metal Hip Implants [Internet]. Medicines and Healthcare products Regulatory Agency. London; [cited 2013 Aug 19]. Available from: http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice–M–T/Metal-on-metalhipimplants/. Stipulates need for annual monitoring of metal-on-metal arthroplasty.

[e] Large head metal-on-metal hip implants “should no longer be used,” surgeons say [Internet]. Arthritis Research UK. 2012 [cited 2013 Aug 19]. Available from: http://www.arthritisresearchuk.org/news/general-news/2012/march/06-mar-large-head-metalonmetal-hip-implants-should-no-longer-be-used-surgeons-say.aspx

[f] Dias J. Metal on Metal Hip Replacements – The Facts [Internet]. British Orthopaedic Association. London; [cited 2013 Aug 19]. From: http://www.boa.ac.uk/PI/Pages/Metal-on-Metal.aspx. Professional organisation stipulation for annual monitoring.

[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

[h] Holzwarth U, Cotogno G. JRC Scientific and Policy Reports: Total Hip Arthroplasty [Internet]. Luxembourg: European Commission; 2012 pp. 1–60. Report No.: JRC72428. Available from: http://ihcp.jrc.ec.europa.eu/our_activities/public-health/hip-prostheses-new-jrc-report/. European Union statement on metal-on-metal arthroplasty ([g] and [h]).

[i] Metal-on-Metal Hip Implants. fda.gov. Silver Spring: US Food and Drug Administration; 2013. FDA statement on metal-on-metal arthroplasty. Available from: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/MetalonMetalHipImplants/ucm241604.htm

[j] Metal-on-Metal Hip Replacement [Internet]. Therapeutic Goods Administration, Department of Health and Aging, Australian Government; 2012 Sep. Available from: http://www.tga.gov.au/hp/information-devices-mom-hip-implants.htm

[k] Metal-on-Metal Hip Implants – Information for Orthopaedic Surgeons Regarding Patient Management Following Surgery [Internet]. Ottawa: Health Canada, Government of Canada; 2012. Available from: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2012/14120a-eng.php. Australian [j] and Canadian [k] statements.