FDA Executive Summary Memorandum

Metal-on-Metal Hip Implant Systems

Prepared for the June 27-28, 2012 Meeting
of the
Orthopaedic and Rehabilitation Devices Advisory Panel
Gaithersburg Hilton
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I. Introduction and Purpose of Advisory Panel Meeting

Hip arthroplasty devices, including metal-on-metal (MoM) hip systems, have been available and in use within the United States for over 50 years. They are frequently used to relieve pain and restore joint function in patients with chronic hip pain or disease which is not responsive to more conservative therapy. All told over 400,000 hip arthroplasty procedures are performed in the United States on an annual basis (***Appendix A***).

With widespread use of these MoM hip systems, more information has become available regarding clinical performance as well as adverse events. Recent data from orthopaedic implant registries as well as peer-reviewed journal publications and presentations at scientific meetings have suggested increases in potential safety issues associated with MoM hip systems including:

1. Local complications such as pseudotumors and aseptic lymphocytic vasculitis-associated lesions ("ALVAL");
2. Early device failure and the need for revision surgery; and
3. Systemic complications from metal ion exposure.

FDA believes that in keeping with its public health mission, it is appropriate to have an open and transparent dialogue among manufacturers, physicians, researchers, the public, and FDA to review currently available data regarding MoM hip systems in an effort to better characterize any potential and real safety risks and generate scientifically-based recommendations for the clinical and patient communities on how to best communicate and mitigate them.

This Advisory Panel meeting is <u>not</u> intended to: (1) reassess the original market entry data; (2) discuss the current or future classification of MoM hip systems; or (3) discuss mandated postmarket studies (i.e., "Section 522" or "post-approval" studies) currently underway for MoM hip systems.

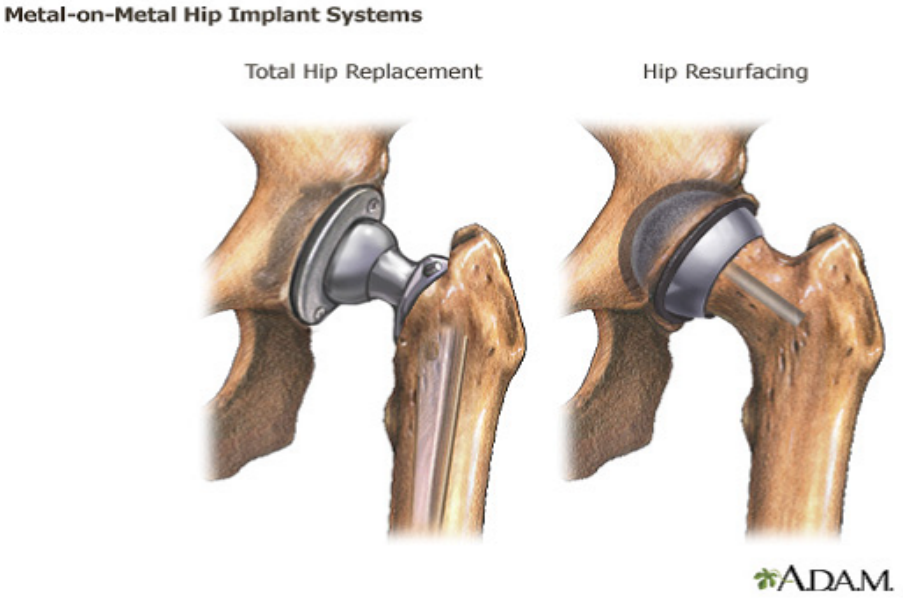
II. Background

<u>Hip Replacement Surgery</u>

Hip replacement surgery involves removing a diseased hip joint and replacing it with a prosthetic joint. In a total hip replacement (THR, also called total hip arthroplasty), the damaged bone and cartilage is removed. The diseased femoral head is replaced with a femoral (hip) component. Most contemporary THR components are 'modular' in nature consisting of multiple femoral and acetabular components. The femoral component consists of a metal stem that is placed into the center of the femur and may be cemented or "press fit" into the bone and a metal or ceramic ball is placed on the upper part of the stem, replacing the damaged femoral head that was removed. The acetabulum socket is replaced with a metal cup which may be lined with a plastic, ceramic or metal insert/liner between the head and socket. Screws or cement are sometimes used to hold the socket in place. The different components allow for different combinations of bearing (articulating) surfaces including ceramic-on-ceramic, metal-on-plastic, and metal-on-metal.

An alternative to THR is hip resurfacing in which the femoral component involves replacement of only the upper surface of the head of the femur. In this surgery, less native bone is removed from the femur as compared to traditional THR surgery. Resurfacing requires stronger bone, so is usually reserved for younger adults.

The image below depicts these two types of surgical procedures.



Hip replacement is most commonly used to treat joint failure or chronic pain caused by diseases or processes such as osteoarthritis, rheumatoid arthritis, avascular necrosis, post-traumatic arthritis, hip fractures, benign and malignant bone tumors, and ankylosing spondylitis. In general, hip replacement surgery is effective in providing pain relief, improving hip function (e.g., increased motion/mobility), and improving activities of daily living.

Hip replacement is usually considered only after other more conservative, nonsurgical therapies have failed. These alternative therapies may include:

- Pain and anti-inflammatory medications
- Glucocorticoid joint injections
- Physical therapy
- Exercise
- Weight loss
- Use of an assistive device (cane, walker)
- Anti-rheumatic medications (for patients with rheumatoid arthritis)

Hip replacement surgery is associated with several, well-characterized real and potential immediate, short-term and/or long-term complications, regardless of the bearing surfaces. These include:

- **Infection**
  Major or deep infections may require surgery and removal of the prosthesis.

- **Venous thrombosis involving leg and/or pelvic veins**
  May potentially be associated with pulmonary embolism.

- **Intra-Operative Nerve injury**

- **Vascular injury/bleeding**

- **Post-Operative Leg-length Inequality**

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- **Dislocation of the head from the socket**
  The risk for dislocation is greatest in the first several months after surgery. A closed reduction may remedy the event, but in some cases where dislocation continues to occur, further surgery may be required.

- **Post-Operative Nerve Palsy (Sciatic, Femoral Nerve)**

- **Implant Wear and Prosthesis Loosening**
  Over time, everyday use of the device may result in wear and loosening. In some cases, loosening may necessitate the need for a revision surgery.

- **Implant Breakage/Fracture**

- **Heterotopic Ossification**
  Extra-articular bone formation involving the tissue around the hip, which may contribute to joint pain and/or stiffness.

- **Post-operative Femoral Neck Fractures** (Resurfacing hip system devices)

Revision surgery, where the artificial joint is replaced, may be required for certain complications and/or after long-term use. In general, revision is considered if medication and lifestyle changes do not relieve pain and disability, or if imaging studies show significant damage to the bone around the prosthesis/joint (e.g., bone loss, wearing of the joint surfaces, or joint loosening). Other possible reasons for revision surgery include fracture, dislocation of the artificial parts, and infection.

Metal-on-Metal Bearings and Current Safety Concerns

Metal-on-metal (MoM) total hip replacement (THR) systems are one of a variety of types of products available for hip replacement surgery and have been available in the United States (US) for several decades. In addition, MoM hip resurfacing devices have been available in the U.S. since 2006.

MoM hip implants provide the ability to use larger diameter femoral head sizes compared to other articulating combinations. These sizes more closely mimic natural anatomy and are intended to improve the stability of the joint. This in turn may reduce the incidence of post-operative dislocation.

First-generation MoM THR prostheses were found to have a higher rate of aseptic loosening and failure than metal-on-polyethylene (MoP) implants and were widely abandoned during the 1970s in favor of MoP devices. Second-generation MoM THR devices (1980s to present) were introduced with the intent to address issues of osteolysis and aseptic loosening noted with MoP devices.

MoM hip resurfacing systems provide for greater preservation of femoral bone stock when compared with conventional stemmed THR systems. Because preserving the femoral neck and shaft allows for a potential revision to a traditional THR should it fail, these devices are espoused to be advantageous for use in younger individuals with higher activity levels. However, the implant procedure for a resurfacing system is felt to be more challenging than for a THR, and has a steeper learning curve.

Device wear is experienced with all types of hip replacement implants over time as the femoral head and acetabular cup components articulate. With a MoM hip system, the articulating surfaces wear and can lead to the production and accumulation of metal ions (e.g., cobalt and chromium) and/or debris within the peri-prosthetic space. Cup malpositioning (e.g., steep inclination angle or altered anteversion) may significantly impact device wear and the local production of metal debris. Different individuals may react differently to the metal ions/debris. Patients may have no significant reaction to these materials. Or there may be a toxic reaction to an excess of metal particles or a hypersensitivity reaction to a normal amount of metal particles. Patients with a reaction to the metal debris may experience a significant inflammatory response which, with time, can lead to peri-prosthetic bone and tissue destruction. The reaction may be referred to by the term "adverse local tissue reactions (ALTR)" or "adverse reaction to metal debris (ARMD)."

These events may result in local complications including bone osteolysis, aseptic lymphocytic vasculitis-associated lesions (ALVAL - histologically diagnosed lymphocytic infiltrations of local tissues), and the development of pseudotumors (radiologically diagnosed peri-prosthetic cystic or solid soft tissue masses containing necrotic tissue). Resulting soft tissue destruction may lead to pain, implant loosening, device failure, and the need for revision surgery. The exact incidence or prevalence of ALTRs is not known. Likewise, the ability to predict which patients will develop ALTRs is not available.

Recent reports in the orthopaedic literature and from international orthopaedic implant registries and professional/scientific meetings have increasingly noted these local complications and cited potential problems of early failure of MoM hip systems, often requiring revision surgery, in a percentage of implanted patients. A comprehensive review of this data is summarized later in this Executive Summary (Sections VII and VIII below).

In addition to local complications, there have been a number of case reports and other manuscripts in the medical literature in which high serum levels of metal ions have been suggested to be associated with systemic symptoms or processes, including effects on the cardiac systems[1], thyroid gland and nervous systems[2], and malignancy[3].

Recent Regulatory Actions Regarding MoM Devices

Emerging data on MoM hip systems have resulted in several actions by regulatory bodies across the world. In December 2009, Australia's Therapeutic Goods Administration (TGA) oversaw the withdrawal of Depuy ASR hip systems from the Australian market after data from the Australian National Joint Replacement Registry (NJRR) showed higher-than-anticipated revision rates for those products.

Shortly thereafter, in April 2010, the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) issued a Medical Device Alert regarding local soft tissue reactions and revision surgery.

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[1] Machado C, Appelbe A, Wood R. Arthroprosthetic Cobaltism and Cardiomyopathy. Heart Lung Circ. Apr 18 2012, http://dx.doi.org/10.1016/j.hlc.2012.03.013.

[2] Tower S. Arthroprosthetic cobaltism: neurological and cardiac manifestations in two patients with metal-on-metal arthroplasty: a case report. J Bone Joint Surg Am. Dec 2010; 92(17)2847-51.

[3] Visuri T, Borg H, Pulkkinen P, Paavolainen P, and Pukkala E. A retrospective comparative study of mortality and causes of death among patients with metal-on-metal and metal-on-polyethylene total hip prostheses in primary osteoarthritis after a long-term follow-up. BMC Musculoskelet Disord. 2010;11:78.

MHRA included recommendations regarding metal ion testing and cross-sectional imaging studies. This was updated by MHRA in February 2012.

In September 2010, FDA met with representatives of the US orthopedic professional societies to gain a better understanding of the current clinical practices in the US for MoM THR and resurfacing hip systems. The discussion with practicing physicians experienced in hip arthroplasty included utilization trends, patient selection criteria, pre-operative patient counseling, follow-up schedule/events, and revision surgery.

In February 2011, FDA posted a public health communication on its website regarding MoM hip systems. This contained a summary of the safety issues with the devices, as well as providing considerations to orthopaedic surgeons for pre-implantation evaluation, intra-operative evaluations, post-operative evaluations and follow-up. It also included considerations for general primary care physicians (regarding potential systemic effects of metal ions) as well as considerations for patients considering hip implants or who have already received a MoM implant. FDA intends to update these considerations based on the Panel Meeting discussion. The current FDA website material is available at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/MetalonMetalHipImplants/default.htm and is provided in ***Appendix B.***

In May 2011, FDA issued orders for postmarket surveillance studies (e.g., "Section 522 studies") to each manufacturer of MoM THR systems requiring them to submit a study protocol to the FDA that addresses specific safety issues related to these devices. Data from the studies will enable FDA to better understand these devices and their safety profiles related to metal ion concentrations in the bloodstream. General information regarding Section 522 studies is provided in ***Appendix C*** and information specific to the MoM THR studies is provided in ***Appendix D.***

As a part of the effort to better understand possible adverse events associated with metal debris from MoM hip systems, FDA has continued its review of published literature, Medical Device Reports (adverse event reports) submitted to the Agency, post-approval study reports and data from several orthopaedic device registries from within and outside the US.

In May, 2012 Health Canada issued a public health communication to orthopaedic surgeons and patients regarding MoM hip implants.

The MHRA and Health Canada communications are provided in ***Appendix E.***

Within the United States, two significant device recalls have taken place for MoM THR systems. This includes the 2008 Class II voluntary recall of the Zimmer Durom Acetabular Component ("Durom Cup") because of inadequate instructions for use, and the 2010 Class II recall of the Depuy ASR Total Hip System due to higher-than-anticipated revision rates noted from outside-the-US joint registries. The recall was for the THR system only as the resurfacing system had not been marketed in the US. The Zimmer Durom device remains on the market in the US with more detailed surgical technique instructions and a surgeon training program, while the Depuy ASR is no longer marketed. Public notifications of those recalls are provided in ***Appendix F***. The recall notifications contained in ***Appendix F*** were generated and distributed by Zimmer, Inc. and DePuy Orthopaedics, Inc., respectively. The information contained therein does not express the views or opinions of the FDA.

III. Regulatory Considerations for MoM Hip Systems in the U.S.

A. Regulatory Classification

MoM THR Systems

MoM THR systems are Class III preamendment devices meaning they were on the market prior to 1976. Although the initial classification panel classified MoM THR systems within Class III, a call for Premarket Approval applications (PMAs) for these systems has not been proposed. Consequently, although MoM THR systems are Class III, they have been regulated through the 510(k) process as Class III 510(k) devices including a Class III certification.

The initial MoM THR design introduced from each manufacturer was supported by clinical performance data with patient follow-up ranging from one to two years. Significant modifications to a device have also required clinical data in addition to non-clinical bench characterization data.

In 2000, the Orthopedic Surgical Manufacturer's Association (OSMA) submitted a petition seeking downclassification of MoM THR systems (cemented and uncemented) from Class III to Class II to the Agency. At a 2001 public meeting, the Orthopaedic and Rehabilitation Devices Advisory Panel recommended by a vote of five to two that the hip joint metal/metal semi-constrained prostheses (cemented and uncemented) not be reclassified from Class III to Class II. In 2002, FDA published a denial of the reclassification petition in the Federal Register. OSMA submitted a second petition for reclassification of MoM THR systems in August 2005, which currently remains open.

In April 2009, the Agency requested information from industry to support either reclassification or a call for PMAs for multiple Class III preamendments devices for which the classification process has not been finalized (515(i) call for safety and effectiveness information, 67 FR 16214). In August 2009, five orthopedic manufacturers submitted information recommending downclassification of MoM THR systems and OSMA submitted an amendment to the open reclassification petition. The proposed rule on the classification of MoM THR systems is currently under review in the Agency; however, as noted above, this topic is not the subject of this panel meeting.

MoM Resurfacing Systems

Hip resurfacing systems consisting of a trimmed femoral head capped with a metal covering and a metal cup in the acetabulum are post-amendments (on the market after 1976) Class III devices regulated through the PMA process. As a PMA each manufacturer must demonstrate the safety and effectiveness of their MoM resurfacing system through stand-alone non-clinical and clinical performance data.

A condition of approval for each of these PMAs include post-approval studies looking at long-term outcomes, in addition to outcomes associated with general use of the devices. These studies are collecting metal ion levels on patients implanted with the devices. A summary of the study designs are included in ***Appendix G*** and the status of these studies is publicly available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm. Training programs were also implemented as a condition of approval for each of the PMAs.

B. Indications for Use

The typical indications for use and contraindications for MoM systems are denoted below.

THR Systems

MoM THR systems are typically indicated for use in total hip arthroplasty in skeletally mature patients with the following conditions:

1. Non-inflammatory degenerative joint disease (NIDJD) such as osteoarthritis, avascular necrosis, post-traumatic arthritis, ankylosis, protrusio acetabuli, and painful hip dysplasia;
2. Inflammatory degenerative joint disease such as rheumatoid arthritis;
3. Correction of functional deformity; and,
4. Revision procedures where other treatments or devices have failed.

MoM THR systems may include the following contraindications:

1. Bone or musculature comprised by disease, prior infection, or prior implantation that cannot provide adequate support or fixation for the prosthesis;
2. Any active or suspected infection in or about the hip or distant foci;
3. Skeletal immaturity;
4. Metal sensitivity;
5. Patients who are pregnant or who may become pregnant; and,
6. Patients with known moderate to severe renal insufficiency.

Resurfacing Systems

Hip resurfacing arthroplasty is intended for reduction or relief of pain and/or improved hip function in skeletally mature patients having the following conditions:

1. Non-inflammatory degenerative arthritis such as osteoarthritis, traumatic arthritis, avascular necrosis, or dysplasia/developmental dislocation of the hip (DDH); or
2. Inflammatory arthritis such as rheumatoid arthritis.

Resurfacing systems are intended for patients who, due to their relatively younger age or increased activity level, may not be suitable for traditional total hip arthroplasty due to an increased possibility of requiring ipsilateral hip joint revision.

MoM Resurfacing systems in general are contraindicated for:

1. Patients with active or suspected infection in or around the hip joint.
2. Patients who are skeletally immature.
3. Patients with bone stock inadequate to support the device.
4. Patients with severe osteopenia. Patients with a family history of severe osteoporosis or severe osteopenia.
5. Patients with osteonecrosis or avascular necrosis (AVN) with >50% involvement of the femoral head (regardless of FICAT Grade).
6. Patients with multiple cysts of the femoral head (>1cm).
7. Patients with any vascular insufficiency, muscular atrophy, or neuromuscular disease severe enough to compromise implant stability or postoperative recovery.
8. Females of child-bearing age due to unknown effects of metal ion release on the fetus.
9. Patients with known moderate to severe renal insufficiency.
10. Patients who are immunosuppressed with diseases such as AIDS or persons receiving high doses of corticosteroids.
11. Patients who are obese and/or with a BMI>35.
12. Patients with known or suspected metal sensitivity (e.g., jewelry).

C. MoM Hip Systems Available in the US and their Characteristics

MoM THR Systems

As of April 30, 2012 FDA has cleared one hundred and eighty-seven (187) 510(k) submissions for MoM THR systems from 21 manufacturers since the late 1970s. Many of the 510(k) submissions are for additional components or modifications to previously cleared systems, so it should not be inferred that there are 187 distinct MoM THR systems. To see the specific indications and a device overview of a cleared MoM THR, please visit the 510(k) Database and search for Product Code 'JDL' for a cemented MoM THR or 'KWA' for an uncemented MoM THR. The database is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

Over time the technology and/or manufacturers have been purchased by other manufacturers or the devices are no longer marketed. There are now five manufacturers that currently legally market MoM THR systems in the US:

1. Biomet, Inc.
2. DePuy Orthopaedics, Inc.
3. Encore Medical, L.P.
4. Wright Medical Technology, Inc.
5. Zimmer, Inc.

Many of these manufacturers, as well as others, market a variety of MoM hip systems around the world. Based on different regulatory jurisdictions, practice of medicine, patient populations, surgeon preference, manufacturing, marketing, etc. there are often distinct design differences in devices marketed in the US in comparison to a product marketed under the same name in other parts of the world. As a result, every country has its own unique product landscape.

MoM THR systems include either a monoblock acetabular shell or a modular acetabular system with a metal liner fitting into the acetabular shell. Some designs include a metal insert on a polyethylene liner in the acetabular shell, also known as a 'poly sandwich' design. The articulating liner is generally manufactured from cobalt-chromium-molybdenum (CoCrMo) alloy conforming to either American Society for Testing and Materials (ASTM) F1537 (wrought) or ASTM F75 (cast)[4]. Most of the CoCrMo alloys have a high carbon content, defined as 0.15 – 0.35 mass percent chemical composition. The minimum/maximum nominal inner diameter of the articulating component may range from 28 to 60mm. The bone facing side of the shell may be titanium alloy (ASTM F136) or CoCrMo alloy (ASTM F1537 (wrought) or ASTM F75 (cast)). The nominal outer diameter of the shell typically ranges from 44 to 80mm in diameter. The outer shell may be cemented for fixation. Many press-fit acetabular shells have a porous or non-porous metallic coating with or without a calcium phosphate coating for uncemented fixation.

The femoral head may be manufactured from CoCrMo alloys conforming to either ASTM F1537 (wrought) or ASTM F75 (cast). Most materials have a high carbon content, defined as 0.15 – 0.35 mass percent chemical composition. Femoral head diameters range from 28 to 60mm in nominal diameter with a wide range of neck offsets. Larger head sizes may have a taper sleeve adapter as an added modular connection between the femoral head and stem increasing the range of offsets available. Femoral stems are generally manufactured from CoCrMo alloy (ASTM F1537 or ASTM

[4] FDA often relies on voluntary conformance with consensus standards, such as ASTM, (developed with representatives from industry, academia and government) to streamline the premarket review process by recognizing consensus material specifications, test methods, and/or acceptance criteria.

F75) or titanium alloy (ASTM F136). The diametrical clearances (nominal) of the systems range from 50 to 250 μm.

Resurfacing Systems

There are currently three MoM resurfacing systems approved in the US:

1. Smith & Nephew Orthopaedics, Inc. Birmingham Hip Resurfacing (BHR) System approved May 9, 2006, P040033.
2. Corin Medical, Ltd. Cormet Hip Resurfacing System approved July 3, 2007, P050016.
3. Wright Medical Technology, Inc. CONSERVE Plus Total Resurfacing Hip System approved November 3, 2009, P030042.

Please see ***Appendix H*** for the Summary of Safety and Effectiveness Data (SSED), Patient and Physician Labeling for the resurfacing systems.

The Smith & Nephew Birmingham Hip Resurfacing System was discussed by the Orthopaedic and Rehabilitation Devices Advisory Panel on September 8, 2005 and the Corin USA Cormet Hip Resurfacing System was discussed by the Orthopaedic and Rehabilitation Devices Advisory Panel on February 22, 2007.

The resurfacing femoral heads range in nominal diameter from 36mm to 58mm composed of cast CoCrMo alloy (ASTM F75) intended for cemented fixation. The cast CoCrMo alloy acetabular shells (ASTM F75) range in nominal outer diameters from 44mm to 66mm with a metallic coating while some also have calcium phosphate coatings.

D. Resurfacing Risk Factor Analysis

As more information is gathered on MoM hip resurfacing systems during the PMA approval process, manufacturers have been better able to evaluate the risk factors associated with increased risk of device failure. Each resurfacing manufacturer has conducted a comprehensive risk analysis based on the outcomes of their clinical study. The most recent risk analysis was conducted by Wright Medical Technology for the CONSERVE Plus Total Resurfacing Hip System (P030042) prior to PMA approval in 2009. Please see the SSED in ***Appendix H*** for the methodology and the complete risk analysis. Analysis of a key set of variables led to the determination of risk factors. A variable was deemed a risk factor if findings of at least one retrieval specimen (out of 37 analyzed) suggested failure due to that variable. Variables meeting the definition of risk factor from those analyses included:

1. Diagnosis of traumatic arthritis, congenital hip dysplasia, or avascular necrosis,
2. Large (>1cm) and/or multiple femoral cysts,
3. Poor bone quality such as loss of femoral head bone,
4. DEXA scan showing severe osteopenia,
5. Femoral neck notching during implantation,
6. Impacting femoral component beyond surgical technique recommendations,
7. Failing to suction excess blood or bone debris before femoral component implantation,
8. Too few or too many drilled holes in top of femoral head along with chamfer holes,
9. Incomplete removal of cystic debris in femoral head,
10. Removal of anterior osteophyte,
11. Too much bone removal either on the acetabular or femoral side,
12. Loss of acetabular press-fit either during initial operation or post-operatively,
13. Improper distribution of cement,

14. Leaving the femoral component proud on the femoral head; and
15. Malpositioning of the acetabular component ($<30^o$ or $>60^o$).

The following risk factors were also identified based on clinical data collected within the study showing an increased likelihood of revision:

1. Patients who are female gender;
2. Patients requiring a small femoral component (≤ 44mm);
3. Patients within the first 60 procedures of a surgeon's cases;
4. Patients diagnosed with avascular necrosis, traumatic arthritis, congenital hip dysplasia, rheumatoid arthritis;
5. Patients with any previous treatment to the hip;
6. Patients with multiple femoral cysts;
7. Patients with an acetabular component position of $< 30^o$; and
8. Patients with any other joint involvement.

For the Corin Cormet Hip Resurfacing System (P050016) the following risk factors were identified as leading to an increased likelihood of revision:

1. Patients who are female gender;
2. Patients requiring a small femoral component (≤ 44mm);
3. Patients with a diagnosis other than osteoarthritis (e.g., AVN, RA);
4. Patients with significant leg length discrepancy (≥ 1cm); and
5. Patients with a baseline Harris Hip Score in the lowest quartile of function.

For the Smith & Nephew BHR (P040033) the sponsor found a marginally statistically significant difference in 5-year survival probability between the patients with Osteoarthritis and Avascular Necrosis as their primary diagnostic indication.

E. Pre-Market Non-Clinical Performance Testing of MoM Hip Systems

Bench testing of THRs has been fairly well developed and standardized over the last 40 years. MoM hip systems were developed on the principle that with precise control of dimensions and clearance, these devices could operate in a way that part of the load at the hip is distributed to the lubricating synovial fluid film, and part of the load to the contacting bearings, which may themselves become coated in a surface layer of synovial fluid proteins (solid lubricant). Under these conditions, in combination with appropriate implant positioning (i.e., positioning that results in concentricity between the femoral head and acetabular cup centers), steady state wear of MoM bearings was expected to be very low. This phenomenon of low wear was also demonstrated with larger size MoM bearings in simulations; larger size bearings are an attractive option for addressing dislocation, which has long been one of the most common failure modes for hip arthroplasty. However, less than optimal clinical outcomes and adverse events reported in Medical Device Reports to FDA have shown that traditional non-clinical testing of MoM hip systems may not be as predictive of clinically relevant failure modes as with other articulating surfaces.

For MoM THR systems, the original MoM THR design from each manufacturer included clinical data with patient follow-up duration ranging from one to two years. Significant modifications to the device have also required clinical data in addition to non-clinical/bench performance testing. As

manufacturing of MoM hip systems significantly influences outcomes, the characterization of finished components is essential. These are common device specification parameters provided to FDA for MoM hip systems:

- Material specifications for manufactured form
- Diameter with tolerances
- Diametrical clearance with tolerances
- Surface roughness
- Sphericity
- Taper dimensions (for MoM THR hips)
- Acetabular liner and shell thickness
- Degree of acetabular cup coverage
- Physiochemical, microstructural, and mechanical coating characterization (metallic coatings and calcium phosphate coatings)

The FDA has seen the following bench performance testing of MoM hip systems:

- Hip simulator wear testing
- Frictional torque (in flexion-extension and in internal-external rotation)
- Range of motion
- Luxation

The FDA has seen the following bench performance testing for acetabular components:

- Cup deformation testing
- Fatigue testing
- Modular cup connection tests (torque-out, lever-out, push-out)

Femoral component testing for MoM THR systems has included:

- Fretting/Corrosion testing (between head, taper, stem)
- Assembly testing
- Pull-off disassembly testing (femoral head to femoral neck; femoral neck to femoral stem)
- Proximal and distal stem fatigue testing

Testing of the femoral component for MoM resurfacing heads has included fatigue testing of the short stem.

The American Society for Testing and Materials (ASTM) recognizes the need for standardization for many test methods for MoM hip systems. ASTM held a 2011 Workshop and a 2012 Symposium on MoM Total Hip Replacement Devices. The program and abstracts for the 2012 Symposium were submitted as part of the Public Docket and are included as part of ***Appendix M***. ASTM is currently developing an overall guide on MoM and ceramic-on-ceramic THR bearings, and test methods on frictional torque testing, high demand wear testing, modular cup fatigue testing, wear/corrosion product analysis and retrieved device wear.

IV. Evaluation of MoM Device Failure Modes

When evaluating the mechanical and electrochemical failure modes of MoM hip systems, some of the primary areas of focus have been loosening of the acetabular cup, wear generation, ion release and (in

MoM THR systems) corrosion of the femoral head/stem junction.[5] On-going research through retrieval analyses into MoM hip failure mechanisms continues and will improve our understanding of the conditions *in vivo* that may contribute to poor mechanical performance of these systems. A more in-depth understanding will enable us to develop more appropriate bench testing and to potentially identify additional risk factors for poor performance. Currently, it is commonly recognized that a poorly positioned acetabular cup quickly leads to impingement and/or edge loading, which can potentially increase wear generation by orders of magnitude. Loosening of the acetabular cup can increase frictional torque also leading to device failure. In addition, there have been recent concerns that the mechanical demands at the modular MoM total hip femoral junctions lead to enhanced wear and mechanically assisted corrosion at the head/stem junction[6]. Concern is developing that metal debris from the taper can cause soft-tissue reactions. For resurfacing MoM hip systems, femoral neck fracture is one of the most common catastrophic failure mechanisms. Gathering information from these and other failure mechanisms may help to optimize bench performance testing to minimize risks.

Dr. Steven Kurtz of Exponent will be discussing these and other potential failure modes during the Panel Meeting (See ***Appendix N for biography***).

V. Soft Tissue Imaging of the Hip

Imaging plays an important role in the evaluation of patients with MoM hip systems. Simon Ostlere provides a review on "How to Image Metal-on-Metal Prostheses and Their Complications" in a September 2011 publication in the American Journal of Roentgenology[7]. Radiographs will identify fracture and loosening, but cross-sectional imaging is usually required to diagnose and stage periprosthetic reactive masses. Masses can be detected with Ultrasound, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). Ultrasound is an effective screening tool as it is not affected by artifacts from metal components; however, ultrasound is not a standard assessment tool in musculoskeletal clinical practice and can be operator dependent. Masses may also be identified on CT, with scatter-reduction protocols, although it exposes patients to ionizing radiation.

With MRI, the extent of the disease and relationship of the abnormality to normal structures associated with an adverse local tissue reaction (ALTR) may be identified. MRI parameters should be optimized to reduce metal artifact as much as possible while maintaining adequate image quality. American Society for Testing and Materials (ASTM) is developing a "Standard Guide to Optimize Scan Sequences for Clinical Diagnostic Evaluation of Metal-on-Metal Hip Arthroplasty Devices using Magnetic Resonance Imaging" to aid in the imaging of masses.

Soft tissue imaging of the hip may be the most effective means to identify a soft tissue reaction in a patient. The Panel will be asked to consider the role of imaging in following symptomatic and asymptomatic patients with MoM hip systems over time, the key findings to look for and if there are recommendations for specific imaging modalities and/or protocols.

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[5] Ebramzadeh E, Campbell PA, Takamura KM, Lu Z, Sangiorgio SN, Kalma JJ, De Smet KA, and Amstutz HC. Failure modes of 433 metal-on-metal hip implants: how, why and wear. Orthop Clin North Am. 2011 Apr; 42(2):241-50.

[6] Fricka KB, Ho H, Peace WJ, and Engh CA Jr. Metal-on-Metal Local Tissue Reaction Is Associated With Corrosion of the Head Taper Junction. J Arthroplasty. May 2012, http://dx.doi.org/10.1016/j.arth.2012.03.019.

[7] Ostlere S. How to Image Metal-on-Metal Prostheses and Their Complications. Am J Roentgenol. Sept. 2011;197:558-567.

Dr. Young-Min Kwon, Director of the Massachusetts General Hospital Center for MoM THR, will be discussing soft tissue imaging modalities and the role of imaging in following patients with MoM hip systems during the Panel Meeting. (See ***Appendix N for biography***)

VI. Issues Pertaining to Metal Ion Testing Methodology

Because of concerns about systemic metal ion toxicity in patients with MoM hip systems, some have advocated for metal ion testing of certain patients with these devices. However, there are not good performance characterization data (for example data on the precision, reproducibility and trueness) available for these tests in the United States. Furthermore, how a test result should be interpreted and incorporated into the management of patients with MoM hip systems has not been clearly defined.

In February 2012, the United Kingdom's (U.K.) Medicines and Healthcare products Regulatory Agency (MHRA) published a medical device alert with updated advice on the management and monitoring of patients implanted with MoM hip systems that includes chromium and cobalt blood tests for certain patients. According to the management recommendations, revision should be considered in a patient if imaging results are abnormal and/or if the whole blood metal ion levels (i.e. chromium and cobalt) are greater than 7 parts per billion (ppb) and rising.

Measuring metal ions, in particular chromium and cobalt, released from the implant has been suggested to be clinically useful in assessing the performance of the hip. Test results have been used to screen patients for significant or continuing implant wear. They have also been used to attempt to determine if the metal ion levels in patients have reached toxic levels. They have been used to attempt to predict adverse patient reactions to the metal ions (for example soft tissue reactions at the joint) and/or to attempt to predict the potential need to revise the patient's implant[8]. At this time, however, we are unaware of rigorous scientific data in the United States supporting or delineating the appropriate clinical use, sample type(s), patient type(s), or medical decision threshold(s) of metal ion testing in patients with MoM hip implants.

Chromium and cobalt can be measured in different sample types including whole blood, serum, plasma, erythrocytes and urine. Chromium and cobalt ions are most often measured using inductively coupled plasma mass spectrometry (ICP-MS) using collision/reaction cells, or by high resolution ICP-MS. However, several aspects of these techniques can make obtaining true and precise measurements of chromium and cobalt difficult.

To justify the incorporation of metal ion testing in the clinical management of patients with MoM hip implants in the United States, the clinical use of these tests needs to be well defined. That is, we need to understand whom the physician will test (e.g., symptomatic patients, asymptomatic patients, patients with resurfaced hips and/or patients with total hip replacements) and how the test result will be used by the physician. The clinical application(s) will drive the performance requirements of the testing methods. Several challenges associated with the methods for measuring and interpreting cobalt and chromium in patient samples need to be resolved or accounted for if these measurements are to be used to impact the medical management of patients with MoM hip implants in the United States. We have identified the following:

[8] Sampson B and Hart A. Clinical usefulness of blood metal measurements to assess the failure of metal-on-metal hip implants. Ann Clin Biochem. March 2012;49(Pt 2):118-31.

1. Clinical decision points for test interpretation are not clearly defined. It is important to determine specific cobalt or chromium levels as a component in making medical decisions for patients that have received these implants in the United States. Furthermore, it is important to properly validate any decision thresholds in order to safely use these values in making medical decisions. The appropriate patient population for such testing needs to be clearly defined in order to ensure that any or all decision thresholds are appropriate and safe for the patient population. To the best of our knowledge, such data have not been generated in the United States. Furthermore, valid reference ranges (or expected values) for cobalt and chromium should be established in the United States population. Properly estimating "normal" values of these ions in the United States population in the different sample types (e.g., whole blood, serum, and/or urine) is critical in order to understand the levels at which chromium and cobalt should be considered elevated in an implanted patient. Currently, no good reference ranges exist for cobalt and chromium in whole blood and serum. Reference ranges for cobalt in urine have been well established by the Centers for Disease Control and Prevention (CDC) as part of the National Health and Nutrition Examination Survey (NHANES)[9] using a method validated to monitor urine cobalt levels in the general population[10].

2. The accuracy and precision of the available tests is unknown. Currently, there are no FDA cleared or approved tests to measure cobalt or chromium levels in patient samples. Several clinical laboratories perform chromium and cobalt testing in whole blood, serum and urine. However, these methods were developed to detect chromium and cobalt poisoning/toxicity (which likely use higher decision thresholds). Therefore, the performance of these methods may not be appropriate for different clinical applications. Specifically, most of these methods claim to measure cobalt and chromium from 1 to 100 ppb. Based on literature reports, we anticipate that cobalt and chromium levels in the whole blood or serum of many patients with MoM hip systems will be in the 1 to 3 ppb[11] range, and for most patients the levels will be in the 1 to 10 ppb range [12,13]. Therefore, if true and precise measurements at the 1 to 3 ppb (or 1 to 10 ppb) range are crucial, methods optimized and validated for measuring a wide range of cobalt and chromium concentrations may not be appropriate. If the tolerance for measurement uncertainty at the lower 3 to 10% of the measuring range of the tests performed by these laboratories is high, these tests may be inaccurate and imprecise at the levels potentially being assessed for implant patient screening. In order to screen patients with a MoM hip systems, tests designed for monitoring chromium and cobalt may be needed. These tests would need to be designed to accurately and precisely measure chromium and cobalt at low and very low concentrations (in fact, they should be designed to be able to measure "normal" chromium and cobalt levels lower than 1 ppb). However, since the FDA currently does not enforce premarket review requirements on lab developed tests (such as the ones currently providing chromium and cobalt testing in patient samples), the performance of these tests is unknown.

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[9] http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Feb2012.pdf (pp132-135)

[10] http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/UHM_E_met.pdf

[11] Sampson B and Hart A. Clinical usefulness of blood metal measurements to assess the failure of metal-on-metal hip implants. Ann Clin Biochem. March 2012;49(Pt 2):118-31.

[12] Kim PR, Beaulé PE, Dunbar M, Lee JK, Birkett N, Turner MC, Yenugadhati N, Armstrong V, Krewski D. Cobalt and chromium levels in blood and urine following hip resurfacing arthroplasty with the Conserve Plus implant. J Bone Joint Surg Am. May 2011;93 Suppl 2:107-17.

[13] Kwon YM, Ostlere SJ, McLardy-Smith P, Athanasou NA, Gill HS and Murray DW"Asymptomatic" pseudotumors after metal-on-metal hip resurfacing arthroplasty: prevalence and metal ion study. J Arthroplasty. June 2011;26(4):511-8.

3. It is not clear which sample type (e.g., whole blood, serum and/or urine) is most appropriate for testing. The clinical use of the test should be considered when determining which sample type(s) to test since different sample types could provide the physician with different information about that patient. For example, metal ion levels in whole blood or serum of a patient can be very different from metal ion levels in the patient's urine depending on the rate of chromium and cobalt clearance from the blood in that patient. Therefore, it may be necessary to measure the ions in multiple sample types in order to properly manage the patient. Each sample type has advantages and disadvantages. For example, while serum may suffer from fewer potential interfering compounds than whole blood, the intracellular concentration will not be measured if serum is the sample type tested. While urine has a well defined cobalt reference range in the United States population, the values in urine are affected by the clearance rate of the metal ions[14]. Since whole blood is the recommended sample type for tests in the UK, most future data from the UK will be derived in whole blood samples. Another important consideration is that the test result from the same patient is different if measured in serum, whole blood or urine. Therefore, test results from different sample types are not interchangeable and would likely require the establishment of different decision making thresholds for all recommended patient sample types. Furthermore, it is crucial that all interferences (both naturally occurring and from any common medications in the patient population of interest) for each specific sample type be resolved in order to consider the use of that sample type for the management of these patients.

4. The collection of the patient sample needs to be carefully controlled to prevent metal ion contamination of the sample from the testing procedure and/or testing environment. The testing laboratory must use collection devices, containers and consumables validated to be trace-metal-free to also prevent metal ion contamination of the sample (since chromium and other metals are used in the manufacture of these collection devices). "Trace-metal-free" collection tubes are commercially available but they are only validated by the manufacturer for measuring toxic levels of metal ions and may not meet the requirements for different clinical applications of these tests. For example, these tubes may not be controlled by the manufacturer for very low-level metal ion contamination since low level contamination may not significantly impact the results of a very elevated metal ion test result. In contrast, even low levels of metal ion contamination will impact the trueness of test results in the expected range for many patients with hip implants. This is an important consideration since the medical decision thresholds for cobalt and chromium are likely to be in the lower range (that is, 1 to 10 ppb).

5. Test results may not be the same between labs. Because of different standards and methods used, test results from one lab may not be comparable to test results from a different lab. This is an important variable because, due to payor requirements, the ordering physician can seldom choose the laboratory where a specific test is performed. If test results are inconsistent across different laboratories, the interpretation of test results by the ordering physician will be difficult.

6. The test methods used are subject to interferences. Since other ions found in patient samples can generate detection peaks at the same masses monitored for chromium and cobalt, techniques to remove these interfering ions need to be established and validated by the labs to ensure that only chromium and cobalt levels are reported in the test result. Validated techniques may or may not be available for all sample types and different techniques may be required for resolving interferences for cobalt measurements and for resolving interferences for chromium measurements. Different techniques are

[14] Daniel J, Ziaee H, Pradhan C, Pynsent PB and McMinn DJ. Renal clearance of cobalt in relation to the use of metal-on-metal bearings in hip arthroplasty. J Bone Joint Surg Am. April 2010;92(4):840-5.

likely required to resolve interferences in the different sample types (for example, potential interfering compounds will not be the same in blood and in urine). Physicians also need to understand potential confounding factors that could also lead to elevated metal ion levels independent of the implant. These include other implanted metal hardware, occupational exposure to metal ions, renal insufficiency and dietary supplements. These need to be evaluated and accounted for as part of the management of patients with implants.

7. There is currently no proficiency testing program to monitor the quality of these test results in the United States. This type of program would help to assure that high quality results for these tests, which are extremely difficult to develop and run, are generated with continued high quality in all laboratories that offer testing. Though proficiency testing is required for all clinical laboratory tests, in the absence of a specific program, labs often substitute repeat testing to meet the requirement. This type of testing would not generally detect fundamental test bias or imprecision.

All of these issues can potentially make the metal ion test results difficult to interpret clinically and need to be understood and resolved. The Panel will be asked to consider if cobalt and/or chromium testing should be incorporated in the management of patients with MoM hip systems. If so, the panel will be asked to consider the appropriate patient population for the testing; the most appropriate clinical use of the test(s); and the most appropriate sample type(s) to evaluate.

During the Panel Meeting, Dr. Robert L. Jones, Branch Chief of the CDC's Inorganic and Radiation Analytical Toxicology Branch in the National Center for Environmental Health will be discussing the metal ion testing methods. Several other speakers will be discussing the systemic effects associated with elevated metal ion levels. (See ***Appendix N for speaker biographies***)

The panel will be asked to consider all of this information when answering questions.

VII. Analysis of the Scientific and Clinical Literature Pertaining to MoM Device Performance and Adverse Events*

Note: All Tables, Figures, and Attachments cited in Section VII can be found in Appendix J

This portion of the Executive Summary analyzes published clinical literature from January 1, 2005 to April 2, 2012 and evaluates THR and resurfacing MoM systems. The analysis focuses on literature specific to the topics of the panel meeting, as follows:

1. Occurrence and Timing of Revision
2. Occurrence and Timing of Revision Within Subgroups of Interest:
    a. By Sex
    b. By Age
    c. By Metal Ion Level
    d. By Femoral Head Size
    e. By Region (i.e. United States (US), Europe, Australia/New Zealand, and other areas of the world)
3. Occurrence and Timing of Revision Compared with Other Articulating Systems (i.e. MoP, Ceramic-on-Ceramic (CoC), and Ceramic-on-Polyethylene (CoP))
4. Occurrence of Local Adverse Events
5. Occurrence of Systemic Adverse Events

The Medline database and PubMed Central were searched on April 2, 2012 via the National Center for Biotechnology Information (NCBI) PubMed, using the following search strings:

1. (metal-on-metal) AND (((arthroplasty OR replacement) AND ("hip")) OR ("arthroplasty" AND "hip")) AND (neurolog* OR neuro* or neurotox*) = 5 articles
2. (metal-on-metal) AND (((arthroplasty OR replacement) AND ("hip")) OR ("arthroplasty" AND "hip")) AND (cancer) = 25 articles
3. (metal-on-metal) AND (((arthroplasty OR replacement) AND ("hip")) OR ("arthroplasty" AND "hip")) AND (pseudotumor) = 15 articles
4. (metal-on-metal) AND (((arthroplasty OR replacement) AND ("hip")) OR ("arthroplasty" AND "hip")) AND (necrosis or inflammat*) = 102 articles
5. (metal-on-metal) AND (((arthroplasty OR replacement) AND ("hip")) OR ("arthroplasty" AND "hip")) AND (revision) = 175 articles

The final search included: #1 OR #2 OR #3 OR #4 OR #5 above with the following limits activated: Humans; Clinical Trial; Meta-Analysis; Randomized Controlled Trial; Review; Case Reports; Classical Article; Clinical Trial; Phase I, Clinical Trial; Phase II, Clinical Trial; Phase III, Clinical Trial; Phase IV, Comparative Study; Controlled Clinical Trial; Corrected and Republished Article; Journal Article; Research Support; American Recovery and Reinvestment Act; Research Support; NIH, Extramural, Research Support; NIH, Intramural, Research Support; Non US Gov't, Research Support; US Government, Research Support; US Gov't, Non PHS, Research Support; US Gov't, PHS, Validation Studies; and English. No limits were set for date.

A total of 290 unique citations were identified from the final PubMed search. Of the 290 unique citations, 125 articles were excluded during initial screening of titles and abstracts due to being case reports, non-research articles or non-systematic reviews (e.g. practice guidelines or clinical overviews, not written in English, not specific to metal-on-metal, or being published prior to 2005 (see Figure 1, Appendix J). One additional large registry article[1] (published March 31, 2012) was identified during the preparation of this review and added to the group of eligible articles. Thus, the full-texts of 166 articles were further examined for eligibility. During full-text review, 37 articles were excluded due to being non-research articles or non-systemic reviews, non-human studies, not specific to metal-on-metal, or not being a cleared or approved use (Figure 1) . Therefore, the final literature review includes 131 studies, which are listed in Table 1 in Appendix J.

Overview of Studies

Among the 131 articles selected for full epidemiological review, there were 6 randomized control trials[2-7], 117 observational studies[1, 6, 8-122], 3 explant/retrieval analyses[123-125], 1 meta-analysis[126], and 4 systematic reviews[127-130]. Of the observational studies, retrospective cohort study was the most common design. Five of the 129 studies had a multi-national design, 32 were conducted in the US, 38 in the UK, 28 in other European countries, 5 in Australia, 20 were in other countries, and 1 did not report location (Table 1).

In total, 43 studies assessed only THR (Attachment 1), 63 assessed only resurfacing (Attachment 2), and 25 assessed both THR and resurfacing (Attachment 3). Three studies assessed MoM in comparison with other articulating systems, 2 THR and 1 resurfacing.

Revision Surgery

This section will discuss findings related to revision surgery by THR or resurfacing. Attachment 4 summarizes information related to revision surgery.

THR

Among the 68 studies evaluating THR, 24 papers assessed revision rates (Attachment 5). Three of the studies reported registry data. Two of these studies were RCTs, 1 was a systematic review and 21 were observational studies (Table 1). ASR was not excluded from these studies.

Overall Revision Rate

Reported revision rates were variable, with some studies finding no revisions, while others found revision rates as high as 16.7%. The table below presents the number of studies reporting revision rates in one-year intervals over time since implant. The range of revision rates within the studies in each interval is provided. There is not a discernible apparent trend in increasing or decreasing revision rates over time. Further interpretation of this table using comparisons is not recommended as the studies providing source data do not capture the same patients over time, nor are the studies reporting in each timeframe mutually exclusive.

Table 1. Revision Rates Over Time Since Implant for THR

Mean Time Since Implant (Months)	Number of Studies Reporting*	Range of Revision Rates (Point Estimates, %)
6 – <12	1	0.50
12 - <24	3	0.3 – 16.0
24 - <36	4	2.06 – 16.4
36 - <48	4	1.0 – 7.6
48 - <60	2	0.50 – 2.0
60 - <72	10	0.0 – 15.0
72 - <84	2	1.0 – 6.0
84 – <96	4	1.0 -5.3
≥96	6	3.7 – 16.7

*Number of patients and time since implant varies across studies.

Sex

There were 5 studies that identified revision rates by sex. These studies had mean follow-up times of approximately 5 years post implant (one study provided sex-specific rates at 3 and 5 years post implant). Sex-specific revision rates ranged between 0 and 19.8%. The revision rate appeared higher among women in most studies, with one of these studies conducting a statistical test and finding a statistically higher revision rate.

Table 2. Revision Rates by Sex for THR

Author, Year	# of Patients	Mean Follow-Up (Years)	Females	Males	Comparison/ P-value
Bolland, 2011	185	3	5.1%	0%	
		5	11.9%	1.4%	
Corten, 2012	1,000	5	2.7%	2.8%	
Donell, 2010	545	5	19.8%	14.6%	
Latteier, 2011	1,363	5	8.2%	2.7%	P<0.0001
Smith, 2012	40,576	5	5.1%	3.7%	

Age

Among studies reporting ages, the average ages were between 49 and 65 years old[2, 3, 32, 60, 76, 84, 85, 126]. One study included assessment by age[1], and found that in women, the risk ratio for age was 0.98 (95% CI: 0.97-0.99), suggesting that the risk of revision decreases with age. Corten provided rates of failure by age group; these rates are listed below[23]. Although Corten shows a relatively stable and possible decrease in revision rates by patient age, no statistical tests were conducted to evaluate the possible trend.

Table 3. Revision Rates by Age Group for THR

Author, Year	# of Patients	Mean Follow-Up (Years)	Revision Rates by Age Group
Corten, 2012	1,000	5	<55 – 3.0% 55-64 – 2.9% 64-75 – 2.6% >75 – 2.7%

Femoral Head Size

Four studies reported information regarding revision rates by head size. Among these studies, Smith[126] noted increased revisions for both men and women with larger head sizes. Latteier noted clinical differences by sex, with an interaction between sex and head size. Specifically,Latteier stated that, "Head size was smaller in failures for women and larger in failures for men, but this was not statistically significant. "[66]. Gioe 2011 found that head sizes of greater than 32mm were less likely to be revised for dislocation[42]. Bolland found no difference in revision by component size[18].

Table 4. Data Presented for Revision Rates by Femoral Head Size for THR

Author, Year	# of Patients	Follow-Up (Years)	Data Presented Regarding Femoral Head Size
Bolland, 2011	185	5	Difference by size not significant (p=0.77)
Gioe, 2011	2,179 (THRs)	7	Premium THR (MoM, CoC, or CoP) were more often >32mm in size and were less often revised for dislocation compared with Standard MoM THR
Latteier, 2011	1,363	5	Interaction between head size and sex
Smith, 2012	40,576	5	Larger head sizes had higher failure HR for men 1.020 (95% CI: 1.004-1.037) HR for women 1.019 (95% CI 1.001-1.038)

Region

There were 5 US studies, 6 UK studies, 7 other European studies, 6 other single country studies (Japan, Australia, Canada, and South Korea), and 1 multi-region study reporting revision rates for THR. The table below presents the number of studies and range of revision rates reported in the published literature by region. Studies from Japan reported both the lowest rate of revision (0%) and the highest (16.4%)[60, 76].

Table 5. Revision Rates by Region for THR

Region	Number of Studies Reporting	Range of Revision Rates (Point Estimates, %)
United States	5	1 - 16
United Kingdom	6	3.7 – 13.8
Europe (non UK)	7	1.8 – 8.83
Japan	2	0.0 – 16.4
Australia	1	15
Canada	1	2.0
South Korea	1	0
Multiple Regions	1	0.3 – 3.4

Resurfacing

Among the 88 studies that evaluated hip resurfacing surgery, 36 evaluated revision following the surgery (Attachment 4). There were 7 comparative studies in this group, including two RCTs[2, 3] (Table 1 in Appendix J).

Overall Revision Rates

Reported device failure rates ranged from 0% to 73%. The highest revision rates, at 31% and 73%, were seen at 6 and >8 years post-implant in studies of 11 and 22 subjects respectively and thus have limited precision due to the sample size. The next highest revision rate was 15%, seen at five years post-implant in a study of 181 patients. The table below presents the number of studies reporting revision rates over time since implant in one-year intervals. The range of revision rates within the studies in each interval is provided. While the lower end of the range of revision rates increases over time since implant, the upper end of the range neither consistently increases nor decreases. Further interpretation of this table using

comparisons is not recommended as the studies providing source data do not capture the same patients over time nor are the studies reporting in each timeframe mutually exclusive.

Table 6. Revision Rates Over Time Since Implant for Resurfacing

Mean Time Since Implant (Months)	Number of Studies Reporting*	Range of Revision Rates (Point Estimates, %)
6 – <12	3	0.0 – 2.7
12 - <24	5	0.01 – 15
24 - <36	6	0.0 - 3.2
36 - <48	7	0.0 – 5.6
48 - <60	2	5.5 – 8.7
60 - <72	10	0.05 – 14.6
72 - <84	2	6.8 – 31
84 – <96	1	4.3
≥96	3	6.1 - 73

*Number of patients and time since implant varies across studies.

Sex

There were 6 studies that identified revision rates by sex and two other studies that assessed differences in revision rates by sex, without reporting specific rates by sex. Seven studies had mean follow-up times of approximately 3-5 years post implant and one study had a follow-up of 10 years. Sex-specific revision rates ranged between 0 and 27.6% for women and 1.4% and 8.97% for men. In 5 studies, the revision rate appeared higher among women, with one of these studies indicating a statistically higher rate. In addition, Ollivere indicated a relative risk of revision 4.94 (95% CI 1.33-18.31) times as high among women compared to men[87]. One study appeared to have a higher revision rate among men, while another study found no statistically significant difference in revision rates among men and women.

Table 7. Revision Rates by Sex for Resurfacing

Author, Year	# of Patients	Mean Follow-Up (Years)	Females	Males	Comparison/P-value
Amstutz, 2011	923	5	8.60%	2.40%	p=0.0073 for time to revision
Corten, 2010	(Review)	5	6.5%	2.6%	
Gianni, 2011	132	4	2.20%	1.40%	
Kim, 2008	200	3	0	8.97%	P=0.041 for effect of sex
Ollivere, 2009	463	4	nr	nr	RR (F vs M): 4.94 (95%CI 1.33-18.31)
Rylander, 2011	80	5	27.60%	6.64%	
Treacy, 2011	144	10	21.6%	1.9%	
Wera, 2010	92	4	NR	NR	p-value not significant

Age

Only Corten and Revell[23, 96] provided rates of failure by age group; these rates are listed below. While Corten shows an apparent increase in revision rates by patient age, Revell shows an apparent decrease in revision rates with increasing patient age. No statistical tests were conducted to evaluate the apparent trends in these two studies. Three other studies conducted statistical comparisons by age[61, 97, 113], and Kim found that patients with failures were significantly younger than those with resurfacing that did not fail[131]. The other two studies did not find significant differences in revision by age. Overall, among studies reporting ages, the average ages were between 44 and 57 years old[2, 3, 9, 13, 40, 57, 58, 60, 61, 88, 94, 96, 99, 126, 132].

Table 8. Revision Rates by Age Group for Resurfacing

Author, Year	# of Patients	Mean Follow-Up (Years)	Revision Rates by Age Group
Corten, 2010	1,000	5	<55yo – 3.1% 55-64 – 4.1% 64-75 – 5.0% >75yo – 9.9%
Revell, 2006	60	6	30-40 - 4.1% 51-60 -2.7%

Femoral Head Size

There was no consistent definition of large head size across studies. Four studies reported information regarding revision rates by femoral head size. Among these studies, no statistical test was performed in the Corten study, however larger head sizes (>50mm) indicated apparently lower rates of revision at 5 years ($p<0.001$)[23]. McBryde noted an increased risk with decreasing head size[81]. Ollivere noted the mean size of femoral heads was smaller among device failures[87], and Rylander noted that significantly more revisions occurred in head sizes 40-44mm[97], as previously noted in Section III.D (Resurfacing Risk Factor Analysis) above.

Table 9. Data Presented for Revision Rates by Femoral Head Size for Resurfacing

Author, Year	# of Patients	Follow-Up (Years)	Revision Data Presented Regarding Femoral Head Size
Corten, 2010	1,000	5	<44mm – 9% 45-49 – 5.7% 50-54 – 2.2% >55 1.7%
McBryde, 2010	(Review)	5	HR per 4mm decrease: 4.87 (95% CI: 4.37-5.42)
Ollivere, 2009	463	4	Mean size of femoral head 44mm in failures compared to 48 mm in survivors (p=0.002)
Rylander, 2011	80	5	54% of revisions were 40-44mm (p=0.003)

Region

By region, there were 13 studies from the US, 12 from UK, 3 from other European countries, 3 from Canada, 2 from Australia, 1 from Japan, and 1 registry analysis covering multiple regions (one study did not report a revision rate). The table below presents the number of studies and range of revision rates reported in the published literature by region. Patients followed up to 10 years post implant in the US had overall revision rates ranging from 0% to 15% compared to 0% to 9.3% in the UK. Rates in Europe (non UK) were not dissimilar to the UK and US. Smaller studies in Japan and Australia imply higher rates of revision (31% of 22 patients and 73% of 11 patients). However, the highest revision rate among studies with more than 20 patients, and thus greater stability around the estimated rate, was 15%, noted in 190 patients followed 5 years.

Table 10. Revision Rates by Region for Resurfacing

Region	Number of Studies Reporting*	Range of Revision Rates (Point Estimates, %)
United States	13	0.0 – 15
United Kingdom	12	0.0 – 9.3
Europe (non UK)	3	2.7 – 3.6
Japan	1	31
Australia	2	0.86 – 73
Canada	3	3.40 – 7.0
Multiple regions	1	1.6 – 4.6

*Number of patients and time since implant varies across studies

Comparison of THR and Resurfacing

Seven studies evaluated revision rates for both THR and resurfacing. The table below presents reported revision rates for THR and resurfacing in each study. Two studies found higher apparent THR revision rates[13, 24] while resurfacing revision rates were apparently higher in the other five studies[2, 3, 24, 60, 126]. One study compared resurfacing to THR revision rates within a model and found that the risk of revision with resurfacing is 1.72 times as high as with THR.

Table 11. Comparison of THR and Resurfacing Revision Rates

Author, Year	# of Patients	Mean Follow-Up (Years)	THR Revision Rate (Point Estimate, %)	Resurfacing Revision Rate (Point Estimate, %)
Baker, 2011	108	9/10	16.7	9.3
Corten, 2010	1,000	1	0.3	1.6
		5	2.7	3.7
		7	3.4	4.6
Costa, 2011	192	2	2.2	0
Howie, 2005b	24	5	15	63.6
		9	15	73
Kabata, 2011	32	6	0	31
Smith, 2010	4,534	NR	RR (Resurf vs. THR) 1.72 (95% CI: 1.20-2.45)	
Vendittoli, 2010	209 hips	4	2.0	5.5

Revisions in MoM Compared with Other Systems

Three studies were identified, which assessed MoM in comparison with other articulating systems, 2 THR and 1 resurfacing. Stulberg[104] found an 8.2% rate of revision among MoM resurfacing patients compared with 2.0% in CoC THR after two years follow-up. Zijlstra et al. found a 3.1% rate of revision among MoM THR patients compared with 1.0% in MoP THR after five years follow-up[5]. Smith followed patients in a registry for 5 years and found that the revision rate was higher for MoM THR compared with CoC or MoP[1]. ASR was not included in any of the preceding 3 articles.

Metal Ion Levels

Out of 131 articles identified from our literature review, 19 evaluated the concentration of cobalt (Co), chromium (Cr), or both in patients with MoM THR or resurfacing systems. See Attachments 1-3 for the overall study design and findings for these articles. These studies were variable in their design (e.g. RTC vs. cohort); comparison groups (e.g. pre- vs. post-operation and MoM implant vs. control group); substance in which metal ions were measured (serum vs. blood); and units of measurement for metal ions (e.g. nmol/L vs μg/L)

Ion comparisons prior to the implantation or revision

Among the 19 studies evaluating metal ions (Co and/or Cr), 9 papers assessed metal ion level change within the same group of patients. Five studies compared changes in Co and Cr levels preoperative or at the start of follow-up with the Co and Cr levels after a period of follow-up (see Table 12). In addition, 3 studies compared the changes before and after revision (see Table 13). All except one of these studies had apparent increases or statistically significant changes in levels of Co and Cr. More specifically, 4 papers demonstrated increased metal ion levels with postoperative follow-up and 3 articles demonstrated decreased metal ion levels after revision of the MoM implant. Girard reported no relationship between metal ion levels and the follow-up; however, they did not provide statistical analyses for the outcome.

Table 12. Studies that Compared Preoperative and Postoperative Metal Ion Levels
(all measurements unless specified are in µg/L. and serum)

Author	Implant type	Preoperatively	Postoperative	p
Cobalt				
Girard (2011)	THR	NA	6.1-years FU**** N=22 (23 hips)* Mean 1.24 (0.5-186)	NR
Grubl (2009)	THR	N=13 below the LoD** 0.3 µg/l.	N=13 1-year FU Median 1.4 µg/l (0.5- 10.5)	p<0.001 p< 0.001
Yang (2011)***	Resurfacing	N=25 Mean 6.63 ± 3.76 (4.53-9.66)	N=25 2-year FU Mean 23.92 ±7.82 (18.37-30.52)	p=.001 pre-op vs. 6 mo
Zijlstra (2009)	THR	N=17 (hips) Median 0.18 (0.18-1.77)	N=17 (hips) 2-year FU Median 0.77 (0.18-15.57) 5-year FU Median 0.88 (0.29-7.02)	<.001
Chromium				
Maezawa (2010)	THR	NR	N=44 6 Mo; Mean 0.75 ± 0.80 (0.1-3.1) 2Y Mean 1.38 ± 0.83 (0.1-3.5) vs. 3 Y 1.76 ± 1.79 (range; 0.1-9.9) 4 Y 1.60 ± 1.29 (range; 0.3-5.6) 5 Y 1.52 ± 1.08 (range; 0.3-5.5) 6 Y 1.56 ± 1.53 (range; 0.1-9.3) 7 Y 1.68 ±1.28 (range; 0.3-5.3)	p<0.01, trend test
Yang (2011)***	Resurfacing	N=25 Mean 6.91 ± 4.03 (5.37-10-52)	N=25 2-year FU Mean 35.22 ± 8.39 (22.87-43.62)	p=.001 pre vs. 6 mo

*Measured in whole blood
** Limit of Detection
*** Unit of measurement is nmol/L
**** follow-up

Table 13. Studies that Compared Serum Metal Ion Levels Prior to MoM implant Revision and After Revision with non-MoM implant

(all measurements unless otherwise specified are in µg/L.)

Author	Implant type	Prior to revision	After Revision	p
		Cobalt		
Beldame (2009)	THR	Patient 1: at 6 months 167.8 Patient 2: at 18 month: 37.22	Patient 1: at 5 months 7.77 Patient 2: 23.1 at 2 years, 1.66 at 5 years	NA
Ebreo (2011)	THR or Resurfacing	N=25 Mean ± SEM 307.1 ± 99.72*	N=25* 4.2 Y FU*** Mean ± SEM 6.56 ± 1.13	p<0.001
Tower (2010)	THR	Patient 1: at 11mo 35 at 36mo 122 at 43mo 85 Patient2: At 12 mo 24	NR	NR
		Chromium**		
Ebreo (2011)	THR or Resurfacing	N=25 * Mean ± SEM 204.54 ± 44.60	N=25* 4.2 Y FU Mean ± SEM 67.34 ± 37.75	p<0.001
Maezawa (2009)	THR	N= 8 unilateral (6-12 mo after revision) Mean 0.46 ± 0.59 (0.1-1.8)	N=8 unilateral (6-12)mo prior revision) Mean 2.53 ± 1.69 µg/L (range, 0.9-5.0)	p>.05

*the unit of measurement is nmol/L
** measured in whole blood
***follow-up

Ion comparisons between different patient groups

Out of 18 articles, 12 compared metal ion levels between different patient groups. (See tables 14-15).

Eleven articles compared Co levels in MoM THR and/or resurfacing patients with other patient groups. One article[69] compared the differences between unilateral and bilateral patients (See Table 14).

Nine out of 12 articles reported statistically significant higher levels of Co in MoM THR and/or resurfacing groups in comparison to other patients. Two of these articles indicated higher apparent levels of Co in the MoM group without statistical comparisons[7, 114]. One article reported no differences in Co levels, but did not provide statistical results for the findings[133].

Table 14. Studies Comparing Cobalt Levels between MoM THR or Resurfacing vs. any Comparison Group (all measurements unless otherwise specified are in µg/L. and serum)

Author	Implant Comparison	Comparison Group	MoM group	p
Bolland (2011)**	Resurfacing free of revision vs. revision/ awaiting revision	5.2Y[1] N= 168 (171 hips)* Median 136 (31 to 793)	5.2Y N=28 (31 hips)* Median 187(34 to 650)	P=0.001
Grubl (2006)	THR CoC vs. THR MoM	1Y N=15 postoperative Median 0.40 (0.15 to 0.70)	1Y N=13 postoperative Median 1.4 (0.5 -10.5)	NR
Hart (2009)**	Resurfacing	reference series of patients with well functioning implants values are not reported	N= 16 unilateral Median 4.5 (0.5-386.5) N=8 bilateral Median 10.6 (2.6- 72)	unilateral p=0.001 bilateral p=0.012
Hur (2008)	THR normal kidney function vs. kidney failure	3.9Y N=6 Mean 0.1 (0.0–0.4)	3.9Y N=5 Mean 12.5 (0.0–51.6)	p = 0.03***
Laffosse (2011)	Resurfacing no neck thinning vs. neck thinning	1Y n= 6 and n= 18 Mean 0.51 ± 0.21 (0.25—0.8) Mean 0.57 ± 0.22 (0.27—1.2) 2 Y n=7 and n=19 0.47 ± 0.3 (0.2—1.05) 0.57 ± 0.2 (0.31—1.02)	1 Y n=24 Mean 0.57 ± 0.23 (0.25—1.21) 2 Y n=26 Mean 0.55 ± 0.22 (0.2—1.05)	NR
Langton (2010)	THR or Resurfacing asymptomatic vs. Revisions due to ARMD[2]	N=483 Mean 2.67 (0.38 to 228)	N=17 Mean 29.7 (4.95 to 96.6)	p <0.0001
Lazennec (2009)	THA unilateral vs. bilateral	1 y n=84 Median 1.41 (1.04–2.78) 3y n=84 Median 1.69 (1.04–2.46) 5y n=84 Median 1.30 (1.01–2.01) 7 y n=84 Median 1.69 (1.12–3.28) 9 y n=56 Median 1.55 (1.05–2.79)	1yr n=25 Median 1.69 (1.13–4.66); 3y n=25 Median 2.33 (1.66–4.15) 5y n=25 Median 2.82 (1.65–4.69) ; 7y n=25 Median 1.89 (1.35–3.65); 9yr n=15 Median 2.03 (1.09–4.82)	p < 0.05 at 3& 5Y-s
Sauvé (2007)*	Gr[3] -B CoP[4]; Gr- C MoP[5] Gr- D stainless-steel -on- polyethylene; Gr-E osteoarthritis vs. Gr -A MoM	33 Y Gr-B(3) Mean 6.28 (6 to 7.0) Gr-C (3) Mean 4.95 (4 to 6.0) Gr-D (6) Mean 6.64 (5 to 9) Gr-E (8) Mean 7.82 (5to 11)	33 Y Gr-A (n=5) Mean 34.09 (17 to 57)	****p<0.01
Weissinger 2011	CoC[6] THR vs. MoM THR	2Y N=38 median 0.I5 µg/L 25% quintile 0.15 75% quintile 0.4	2Y MoM N=42 median 0.41 µg/L 25% quintile 0.8 75% quintile 2.7	p<0.0001

Williams 2011)****	Normal range vs. MoM THR or Resurfacing	0.030 to 0.400 Trace Elements lab London	n=31 MoM THR Median 4.50 SD 10.46 (0.54 to 58.78) n=20 MoM HR Median 0.83 SD 47.21 (0.39-195.61)	NR
Witzleb (2006)	implant free vs. Resurfacing	2Y N=130 Median 0.25	2Y MTHR[7] n= 60 unilateral Median 1.70 µg/L N= 14 bilateral Median 3.18 µg/L n=111 BHR Median 4.28 µg/L	P<0.001 & P=0.3, MTHR bilateral
Zijlstra (2008)	THR MoP vs. THR MoM	N= 14 (hips) Preoperatively Median 0.24 (0.18-0.65) 2-Y Median 0.18 (0.18-1.06) 5-Y Median 0.30 (0.29-1.65)	N=17 (hips) Preoperatively Median 0.18 (0.18-1.77) 2-Y Median 0.77 (0.18-15.57) 5-Y Median 0.88 (0.29-7.02)	Pre-op p=1.85; 2 Y p<0.01; 5 Y p=0.001

*nmol/L
** measured in whole blood
*** One patient in kidney failure group had Co concentration below LoD
**** excluded outliers had an ion level of >50 µg/L

Abbreviations:
[1] Y- Average number of years since implant
[2] ARMD- adverse reaction to metal debris
[3] Gr-group
[4] CoP-ceramic on polyethylene
[5] MoP- metal on polyethylene
[6] CoC-ceramic on ceramic
[7] MTHR- Metasul total hip replacement

Chromium levels

Nine articles compared Cr level differences in MoM THR and/or resurfacing with other patient groups. One article[69] compared the differences between unilateral and bilateral patients (See Table 15).

Six articles reported statistically significant higher levels of Cr with MoM systems with one article having 5-14 times higher levels of Cr ions[114] . Two articles did not find statistical differences between MoM and reference groups[18, 55]; another article did not find any differences between unilateral patients[48]. Finally one article has reported no differences between comparison groups in Cr ion levels, but did not provide statistical results for these findings[133].

Table 15. Studies Comparing Chromium Levels between MoM THR or Resurfacing vs. any Comparison Group (all measurements unless specified are in µg/L. and serum)

Author	Implant Comparison	Comparison Group	MoM group	p
Bolland (2011)**	Resurfacing free of revision vs. revision/awaiting revision	5.2Y N= 168 (171 hips)* Median 63 (8 to 603)	5.2Y N=28 (31 hips)* Median 87 (34 to 650)	P=0.14
Hart (2009)	Resurfacing	reference series of patients with well-functioning implants values are not reported	N=25 N=16 unilateral Median 3.0 (0.8 to 179.0) N=8 bilateral Median 7.9 (2.3 to 42.1)	unilateral p=0.065 bilateral p=0.0003

Author	Implant Comparison	Comparison Group	MoM group	p
Hur (2008)	Resurfacing normal kidney function vs. kidney failure	3.9Y N=6 Mean 6.4 (2.3–13.9)	3.9Y N=5 5.1 (2.8-9.0)	P = .65
Laffosse (2011)	THA no neck thinning vs. neck thinning	1Y n= 6 and n= 18 Mean 1.73 ± 0.5 (1—2.4) Mean 1.2± 0.7 (0.4—3) 2 Y n=7 and n=19 Mean 1.23 ± 0.62 (0.7—2.1) Mean 1.6± 0.68 (0.6—3)	1 Y n=24 Mean 1.50 ± 0.90 (0.4—4.5) 2 Y n=26 Mean 1.49 ± 0.67 (0.6—3.00)	NR
Langton (2010)	THR or Resurfacing asymptomatic vs. Revisions due to ARMD	N=483 Mean 4.23 (0.58 to 115)	N=17 Mean 33.6 (3.84 to 67.5)	p <0.0001
Lazennec (2009)	THA unilateral vs. bilateral	1 y n=84 Median 2.18 (1.49–3.37 3y n=84 Median 2.05 (0.94–3.21) 5y n=84 Median 1.70 (0.90–3.41) 7 y n=84 Median 1.42 (0.80–2.25) 9 y n=56 Median 1.49 (0.72–2.0)	1y n=25 2.60 (1.45–5.52) 3 yr n=25 2.61 (1.45–5.64) 5 yr n=25 2.83 (1.81–5.48) 7 yr n=25 2.41 (1.73–4.48) 9 y n=15 2.99 (1.97–4.40)	p < 0.05 at 3, 5 & 7 Y
Sauvé (2007)*	Gr- B CoP; Gr -C MoP Gr- D SS-on-polyethylene; Gr-E osteothritis vs. Gr- A- MoM	33Y Gr-B (N=3)20.00 (19 to 21); Gr-C (3) 20.29 (18 to 21); Gr-D (6) 21.52 (20 to 23); Gr-E (8) 19.70 (11 to 25)	33Y Gr-A (5)58.37 (35 to 85)	P<0.01
Weissinger 2011	CoC THR vs. MoM THR	2Y N=38 median 0.I5 µg/L 25% quintile 0.15 75% quintile 0.4	2Y MoM N=42 median 0.41 µg/L 25% quintile 0.8 75% quintile 2.7	p<0.0001
Williams (2011)***	Normal range vs. MoM THR or HR	0.099 to 0.198 Trace Elements lab London	n=31 MoM THR Median 2.82 SD 9.12 (0.66 to 50.47) n=20 MoM HR Median 1.08 SD 34.28 (0.45-142.46)	NR
Witzleb (2006)	implant free vs BHR and MTHR	2Y N=130 Median 0.25	2Y MTHR n= 60 unilateral Median 1.22 µg/L N= 14 bilateral Median 2.50 µg/L n=111 BHR Median 5.12 µg	P<0.001

*nmol/L
** measured in whole blood
*** excluded outliers had an ion level of >50 µg/L

Abbreviations:
[1] Y- Average number of years since implant
[2] ARMD- adverse reaction to metal debris
[3] Gr-group
[4] CoP-ceramic on polyethylene
[5] MoP- metal on polyethylene
[6] CoC-ceramic on ceramic
[7] MTHR- Metasul total hip replacement

Results presented in Table 14 and Table 15 show that MoM patients generally had higher ion levels of Cr and Co in comparison to the reference groups. More specifically, at yearly stages of having the implant (6 months – 2 years) patients with MoM THR or HR have demonstrated higher metal ion levels in comparison to the reference patients. Further, MoM patients demonstrated higher Co and Cr ion levels in comparison to the reference groups at the later stages of having the implant (3-33 years). In addition, Lazennec (2009) demonstrated that bilateral MoM THR patients have higher levels of metal ions in comparisons to the unilateral patients.

Relationship between metal ions and AE

A majority of articles did not investigate a direct relationship between increased metal ion levels and adverse events. Out of 18 articles with metal ion information, 3 assessed the relationship between high metal ion levels and revisions, 2 articles investigated kidney failure and 1 article assessed femoral neck thinning during follow-up.

Bolland (2011) and Langton (2008) found that patients with high Co and Cr levels were at higher risk for revision. In prospective follow-up study of 185 MoM THR patients 17 hips (8.5%) required revisions at average of 45.5 months of the follow-up[18]. Two revisions were due to the deep infection and one due to the periprosthetic fracture, the remaining fourteen revisions were due to the ARMD.The ARMD patients had evidence of high wear and corrosion. At the end of follow-up 14 additional patients were awaiting revision, 10 due to high Co ion levels and radiological changes[18].

In Langton's investigation 17 patients (3.4%) were identified with adverse reactions to metal debris for which revisions were required (all ASR). All patients had higher Co and CR ion levels compared to the non-revised patients[65].

Both late revisions in the RCT were motivated by the high levels of serum Co, combined with pain in one patient and with squeaking in the second patient[134]. In addition, in two other articles, patients with revisions had higher metal ion levels in comparison to those without revision and the CoC group, respectively[34, 48].

In 2 case reports of MoM THR patients undergoing revisions due to local and systemic metal ion adverse reactions[135], symptoms included groin pain, rashes, headaches, tremor, hearing loss, vertigo and dyspnea. Co serum ion levels were 23-122 μ/L prior to revision. Both patients had symptom relief after revisions[135].

However, two studies did not find a relationship between increase ion levels and femoral neck thinning and reported that MoM group had higher rate of luminescence upon radiographic examination in comparison to the CoC group [133, 136].

Additional Reports

While not included in the systematic literature review, a reassessment of the literature for ALTR captured case reports that report on high metal ion levels. A 75 year old farmer presented with possible cobalt cardiomyopathy from severe cobalt poisoning after hip replacement[137]. His condition improved with revision of the hip. Two patients were noted with high cobalt ion concentrations with depression and anxiety after receiving MoM THR and three had similar conditions after resurfacing[135, 138] . The range of presenting serum cobalt ion concentrations was 64-74 mg/L. These patients developed sequelae including tinnitus, vertigo, high frequency hearing loss, early cardiomyopathy, hypothyroidism, and hyperparathyroidism. Four patients received revision with CoP and their serum cobalt levels decreased[135, 138]. Histopathology showed metallosis, necrosis, and chronic inflammation in the four patients[135, 138].

Local Adverse Events

THR

Pain

Two studies in this literature review evaluated pain as an outcome, one resurfacing and one THR. Among 116 patients followed an average of 26 months after resurfacing implant, 18% reported growing pains that limited activity or required medication. Pain score was measured at 5.9 out of 10. A larger proportion of women than men had this problem. X-ray found atrophy of muscles as the cause of pain[17]. In a study of 13 patients with failed metal on metal bearing hip prostheses, groin pain was reported universally[95].

Dislocation

Usage of larger femoral head can reduce dislocation risk. This review identified two studies that evaluated dislocation for THR, outlined in the table below. Sikes, in a US based study that included patients at high risk of dislocation due to history of alcohol abuse, high BMI, hip dysplasia, major pelvic hip surgery, neurologic disease and inflammatory arthritis, compared large head MoM (>38mm) to standard diameter MoP hips[121]. The MoM group had no dislocations or revisions and the MoP had two dislocations with a minimum 2-year follow-up[121]. Radiographic results were similar between both groups.[121] In a French study with a mean 9 year follow-up, Lazennec found two recurrent dislocations out of 109 MoM patients who were revised to MoP due to impingement between the titanium femoral neck and the cobalt-chrome acetabular cup insert[69].

Table 16. Dislocations and THR

Author, Year	# of Patients	Follow-Up (Years)	MoM THR Dislocations/Implants	MoP Dislocations/Implants
Sikes, 2008		Min 2	0/52	2/29
Lazennec, 2009	109	Mean 9	2/109	–

Localized Immune Response

With our initial search criteria, four studies were captured that provided data on local immune response[12, 18, 26, 122] for MoM implants. These studies may indicate that some patients develop a localized immune response (self vs. other) to shed metal particles while other patients may be inherently predisposed to hypersensitivity to metal particles. Willert found that 5 patients with second revisions developed localized immune response with infiltration as well as hypersensitivity to metal[122]. Aroukatos reported that tissues examined in patients with low-carbide (which is atypical of US implants), MoM bearings were associated with classic pathological hallmarks of inflammation:

(1) Extensive necrosis & fibrin exudation in the newly formed hip capsule and
(2) Diffuse and perivascular lymphocytic infiltration of a higher degree than in hips with CoP bearings in conventional histologic examination, and
(3) T > B cells[12].

Davies compared MoM THR with MoP and pre-surgery tissue controls, and found that local immunological reaction was more severe in MoM; evidenced by the presence of B-lymphocytes in tandem with macrophages bearing wear particles[26] (implicating these immune cells as reactive to shed metal particles). Bolland found presence of ARMD in 14 out of 17 device revisions[18] at an average of 45 months post implant

Adverse Local Tissue Reaction (ALTR)

With our initial search criteria, no studies of THR were captured that independently reported specific information on ALTR.

Resurfacing

Dislocation

Two studies were identified that evaluated dislocation for resurfacing. Heilpern reported no dislocations in 377 large diameter hips with a mean follow up of 4 months[50]. Hing reported 10% dislocations in 500 patients with 3 year follow-up[51].

Localized Immune response

Three studies provided data on local immune response[63, 86, 91]. Kwon assessed lymphocytes activity proximal to resurfacing MoM and found no difference in the level of infilterates[63]. Park found patients with early osteolysis had a significantly higher rate of hypersensitivity reaction to cobalt compared with controls[91]. Retrieved periprosthetic tissues showed no evidence of metallic staining, but histologic analysis revealed an accumulation of CD3-positive T-cells and CD68+ macrophages as well as an absence of both particle-laden macrophages and polymorphonuclear cells. Immunohistochemical analysis demonstrated that bone-resorbing cytokines such as IL-1β and TNF-α were produced mainly by infiltrating lymphocytes and activated macrophages[91]. Further, Ng performed a study of wear analysis in 5 explanted devices and showed increased wear at the head interface and corrosion at the stem[86]. Compared to non-MoM devices, the MoM bearings had more perivascular lymphocytic infiltration (PVLI) (59% vs. 18%, $p<0.001$). This correlates with other signs of metal hypersensitivity, but not with histologic measures of metal particulate load[86].

Adverse Local Tissue Reaction (ALTR)

Pseudotumor was assessed in 2 resurfacing studies. Beaulé reported that the incidence of pseudotumor in a group of 3,242 patients was 0.12 % over an average of 3.4 years[139]. Incidence of pseudotumor was reported in a study with 75 patients in three groups. Williams reported the prevalence of asymptomatic pseudotumor after resurfacing, detected with ultrasound, with evaluations occurring more than 2 years after surgery[115]. They found a solid or cystic mass in 32% of MoM THR, 25% of MoM resurfacing, and 4% of MoP. Pseudotumor formation was significantly more frequent in the MoM THR group compared with the MoP group ($p = 0.015$). No significant correlation was found between the serum metal ion levels and the size of ALTR abnormality. Kwon conducted a comparative study with MoM resurfacing patients with ALTR, MoM resurfacing patients without pseudotumor and age matched control patients without MoM implants and no clinical history of metal allergy[63]. They found that pseudotumor was associated with elevated nickel ion levels, but not elevated chromium or cobalt ion levels[63].

Re-assessment of ALTR

Because no studies of ALTR for THR and only a small number of studies for resurfacing were initially identified in the systematic literature review, all article abstracts (including case reports and other previously excluded article types) meeting the PubMed search criteria included below, from 2005 to May 16th, 2012 were re-assessed.

- (metal-on-metal) AND (((arthroplasty OR replacement) AND ("hip")) OR ("arthroplasty" AND "hip")) AND (pseudotumor)
- (metal-on-metal) AND (((arthroplasty OR replacement) AND ("hip")) OR ("arthroplasty" AND "hip")) AND (osteolysis)

- (metal-on-metal) AND (((arthroplasty OR replacement) AND ("hip")) OR ("arthroplasty" AND "hip")) AND (ALVAL)

In this reassessment, 42 articles specific to pseudotumor, osteolysis, and/or ALVAL were identified. The following paragraphs highlight the findings of this reassessment for ALTR associated with MoM THR.

Case reports were published for patients with ALVAL or higher ALVAL scores who also had suspected metal hypersensitivity[140, 141] and pain[142]. Cup loosening, neck thinning, pseudoarthritis, soft tissue loss, and bone destruction with pelvic discontinuity were also found in ALVAL cases[31, 112, 142]. Tissue from patients with pseudotumor-like reaction and suspected higher wear had lower ALVAL scores[141]. However, one study following 635 patients for one year found no pseudotumors or complications related to ALVAL[143] and another case-control study of 50 patients found no difference in the proportion of pseudotumors with and without pain[144].

Pseudotumor occurred in 2 of 75 patients followed for 3 months[145]. However, another study found no pseudotumor in 90 THR patients followed for more than 10 years[146]. Case reports were seen for pseudotumor leading to femoral vein thrombosis[147] and for recurrent pseudotumor with revision to CoC and no subsequent recurrence at 30 months post-CoC implant[148]. Substantial necrosis was observed in periprosthetic connective tissue of 13 pseudotumors[78] as was increased wear in cases of pseudotumor compared with control implants[45].

Osteolysis was not seen in 9 studies which assessed this outcome[16, 25, 149-155]. However, there were 16 case reports[53, 156-158]: osteolysis was the listed reason for revisions in 3 articles[52, 106, 159], and cases of osteolysis were seen in 1%-4% of patients in other studies[22, 43, 134, 160-163]. Osteolysis was observed to be associated with elevated ion serum levels in only one article[6].

Osteolysis did not lead to different survivorship[164]. One article indicated that osteolysis was not correlated to presence of wear particles[165] while two articles did indicate a correlation[12, 13]. Osteolysis was listed as a risk factor for revision in two studies[150, 166]. In other articles, osteolysis was noted in cases of soft-tissue inflammatory reactions[167].

Systemic Adverse Events – THR and Resurfacing

Neurotoxicity and Cancer

Based on our initial search criteria, no studies were identified in the systematic literature review that indicate neurotoxicityor cancer as a result of the use of MoM THR or resurfacing. Therefore, all abstracts meeting the initial PubMed search criteria from 2005 to May 16th, 2012 were reassessed. In this reassessment, only two articles discussed possible neurotoxicity in addition to several case reports of cancer. The following paragraphs highlight the findings of this re-assessment.

Neurotoxicity

While he describes neurological impairments as endemic to older patients undergoing total hip arthroplasty, Tower noted visual system changes and optic nerve atrophy in a patient with a serum cobalt concentration of 122µg/L[135]. A second patient in the same Tower case report exhibited vertigo, cognitive decline, hearing loss in a patient with a serum cobalt concentration of 23µg/L[135]. Tower also describes in a published 2012 letter that 5/5 patients (2 with ASR resurfacing hips and 3 with Birmingham resurfacing hips) exhibited depression and anxiety. In this cohort, 4/5 developed tinnitus, 1/5 developed vertigo, and 4/5 had high frequency hearing loss[138].

Cancer

As a result of the secondary search of cancer case reports following MoM hip replacement, the following cancers were reported: adenocarcinoma[168], angiosarcoma[169, 170], malignant fibrous histiocytoma in area of implant, extra-cranial meningioma[171], osteoma[172], nodular squamous cell carcinoma in a THR revision scar[173], and renal carcinoma[174]. Studies with patient follow-up found the following cancers: low-grade B-cell carcinoma (11.6% of 852)[175], 19 cancers in a retrospective analysis of 6161 femoral heads (possibly some occurrence before THR)[176] and 46 malignant tumors at THR sites found between 1974 and 2003[177]. In one longitudinal study, there was no evidence that incidence of cancer after THR increased[178]. One study indicated no increase in the standardized incidence ratio of cancers after THR compared with the general population[179]. Another did not report an increased risk of cancer from linked records of hospital admissions and death[180]. However, one study did find that the standardized mortality ratio for MoM THR was higher than that for MoP[181].

Studies of Retrieval Analysis

While not the focus of this literature review, 3 studies were identified with the revised search criteria, which reported retrieval analysis based on a cross-sectional study design. Implant history, such as time since arthroplasty, was not described. Braunstein reported a study of 44 McKee-Farrar MoM THR hip prostheses, which were made of cobalt-chromium alloy according to ISO 5832-4, 26 implants having 35 mm diameter, 5 implants having 39 mm, and 13 implants having 41.5 mm diameter.

Soft tissue was examined at retrieval analysis and metallic debris was detected in all 44 patients. This finding was not associated with hip size.[123] Another study compared 66 explanted ASR and 64 explanted BHR[125] resurfacing components. ASR cases showed increased wear of acetabular component compared to BHR. The final study positively associated wear with ALTR formation found 3 times more linear and 6 times more volumetric wear in ALTR (n=56) over a matched control group (n=56): 94% (17/18, odds ratio = 17.16) in the ALTR group had edge wear, compared with 33% (6/18, odds ratio = 0.49) in control group ($p < 0.001$) [182].

Critique and Assessment of Published Literature:

Overall, multiple strengths were identified in the body of literature that was assessed. There were 4 RCTs that evaluated the performance of THR compared with resurfacing or with patients who received a hip with another bearing surface. There were a number of large sized studies, including publications from large registries followed for several years. These larger sized patient cohorts make an especially important contribution to the literature because of their generalizability.

There were a number of limitations identified in the published literature. Many of the studies were retrospective or were case series. Design issues, such as small sample size, lack of a comparator arm, or inadequate statistical analysis made it difficult to extrapolate definitive assessment of MoM THR and resurfacing. Many of the studies were conducted at a single site or by a single surgeon. Additionally, a subset of papers from outside the US included implants that are not currently available in the US. Consequently, differences in MoM devices and practice of medicine around the world may limit generalizability across regions.

Revision

Revision was included in the evaluation of 24 studies of THR and 36 studies of resurfacing. These studies presented data on revision at varying time points from 6 months to more than 10 years post-implant. However, few studies followed a large number of patients over time, allowing for cumulative assessment of revision over time since implant. This was most often seen in large registry studies. Evaluation of revision over time from registries is best assessed by leveraging the data from the multiple registries in the International Consortium of Orthopedic Registries (ICOR) (see Section VIII).

Studies reported data from a variety of regions, surgical sites and analyzed a variety of devices, giving a richer perspective of the experience with MoM hips throughout the world. However, there were few studies that evaluated specific areas of concern such as differences in revision rates by sex, age, metal ion levels or head size.

Local Adverse Events

In comparison to the number of studies on revision, very few studies assessed local adverse events. Six studies presented data on local adverse events with THR and 6 presented data for resurfacing. Due to the small number of patients in the studies presenting data for localized immune response, caution should be used in interpretation and generalization to other populations. Assessment of pseudotumor for resurfacing was presented in comparison to MoP in one study, and to patients without hip implants in another study, indicating differences from other patient populations. A broader view and reassessment provided a small number of case reports and limited studies evaluating ALTR. Dislocation rates were variable and likely related to the patient population being assessed. While there are reports of adverse local events such as low Harris Hip score, inflammation, and other quantitative and qualitative measures, in this systematic review of the published literature, insufficient data was identified on these topics to quantify the incidence of these adverse events.

Systemic Adverse Events

No studies were identified, which presented primary evaluation of key systemic adverse events of interest, namely neurotoxicity, tissue necrosis, and cancer. Re-assessment of the literature provided a small number of case reports and limited studies of cancer recurrence. While overall findings are mixed, there is some reported concern in the literature that there are incidences of cancer in patients receiving metal-on-metal total hip implants. Of note, a large registry study was published in April 2012, which found no evidence that incidence of cancer increased after MoM THR.

Conclusions:

This review evaluated the published literature captured in the systematic search for the current generation of MoM hip devices for THR and resurfacing. Studies selected for this review were conducted in both US and outside the US regions.

Based on the identified literature, the rate of revision for MoM is likely not lower than the rate of revision for other articulating surfaces. Rate of revision may be higher with resurfacing compared to THR and women may be more at risk of revision than men. However, differences in revision by age, ion level and femoral head size are less well described.

Known local adverse events, among others, include localized immune response, ALTR, and dislocation. While these outcomes are known, their occurrence rates and severity were not well defined in the identified literature. Pain and tissue necrosis were noted with revision, but also among other MoM patients without these specific findings. Primary studies for systemic outcomes of interest such as neurotoxicity, cardiomyopathy, endocrine symptoms, and cancer were not identified.
While many studies on MoM THR and resurfacing exist, the clinical literature on specific subgroups of

interest and rarer outcomes is minimal. Revision risks from small clinical studies are bolstered by findings from longer-term registry data. However, current registries do not assess local and systemic adverse events.

VIII. Data from the ICOR Registries

The published literature reviewed above includes peer-reviewed publications of registry data. These registries provide a substantial proportion of the literature. However, through the efforts of the International Consortium of Orthopedic Registries (ICOR), there is additional, unpublished registry data presented below.

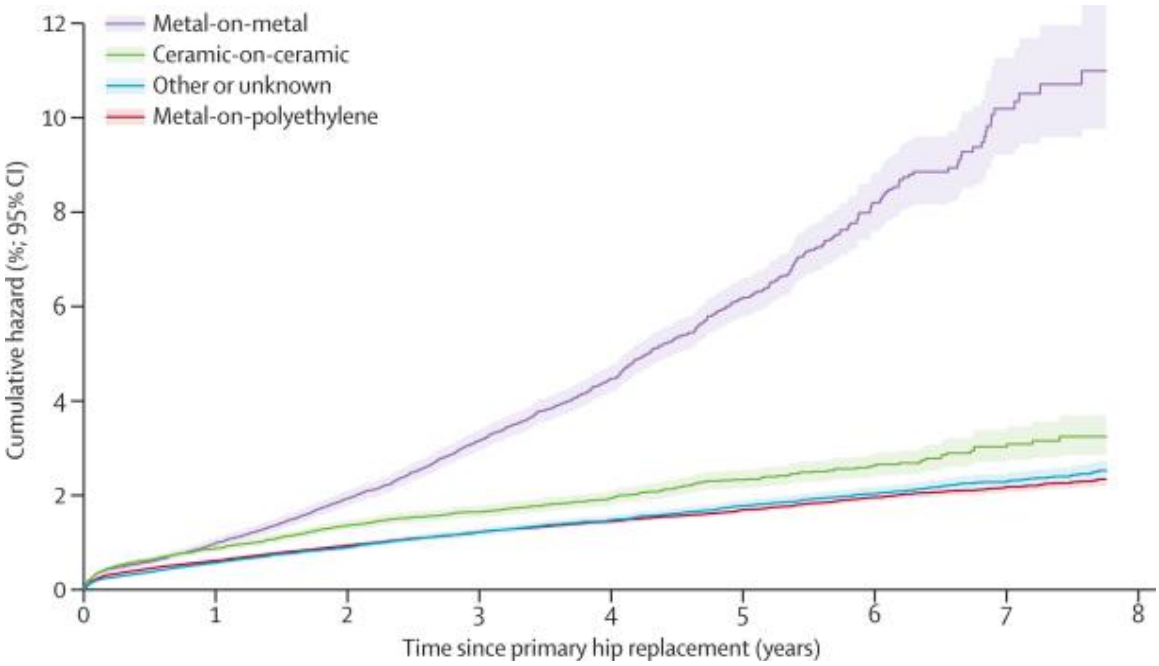
FDA/CDRH launched the "International Consortium of Orthopedic Registries Initiative" (ICOR) in 2010, with the strategic goal of establishing a scientific infrastructure across registries, based on a distributed consortium of national and international orthopedic registries. Such an infrastructure will serve as a platform for robust studies of performance of orthopedic implants, including comparative studies. The consortium consists of 29 registries from 14 nations. Combined, the ICOR registries capture more than 3,500,000 orthopedic surgical procedures. Please see ***Appendix K*** for additional information related to the ICOR effort.

England and Wales National Joint Registry

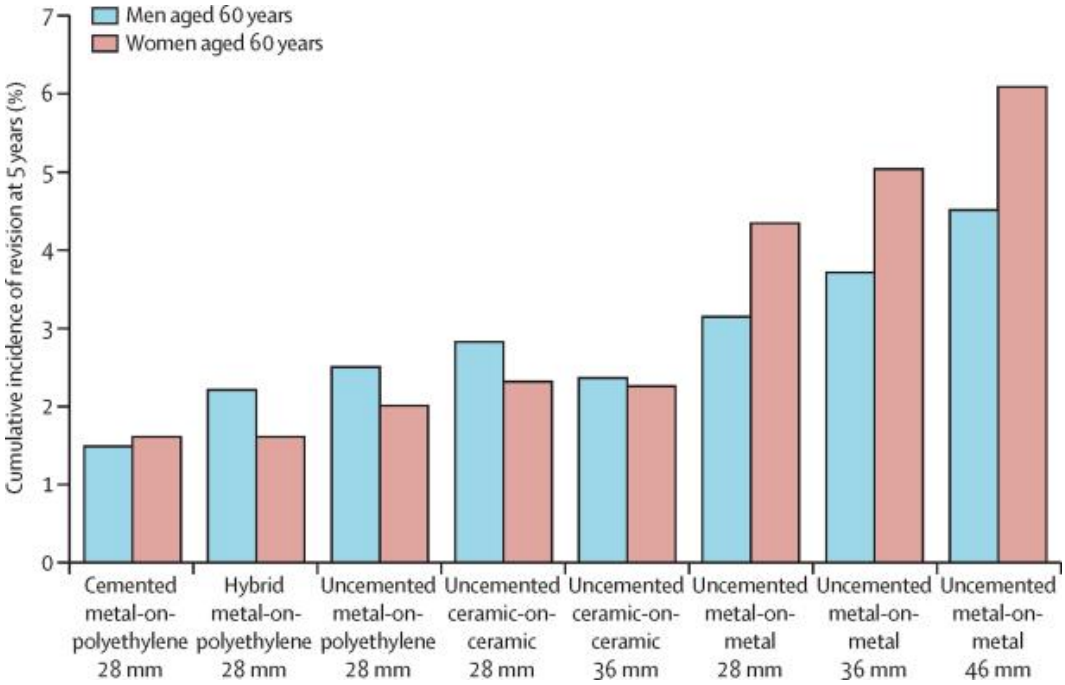
The England and Wales National Joint Registry began collecting data on hip and knee replacement operations on April 1, 2003. The work of the NJR is funded through a levy raised on the sale of hip, knee and ankle replacement implants. Between April 1, 2003 and March 31, 2011, 1,082,932 procedures were submitted. Of 518,731 hip procedures, 466,967 were primary hip replacements and 51,764 were revision hip replacements.

All patients had American Society of Anesthesiologists (ASA) grade 1 or 2 at time of primary surgery and the diagnosis was osteoarthritis only. In addition, ASR implants were excluded from the main analyses. Analyses is for conventional hip replacement only (hip resurfacing is excluded). Multivariate flexible parametric survival models that estimate the cumulative incidence of revision in the presence of the competing risk of death were used for the analyses. In all models, head size and age were selected as predictors of revision and age as a predictor of death for the competing risk. Separate models were estimated for men and women and for the deferent bearing groups: metal-on-metal, ceramic-on-ceramic, and the three metal-on-polyethylene groups (uncemented, cemented, and hybrid fixation).

The 5-year revision rate for MoM implants was 6.2% (95% CI, 5.8–6.6) which was almost three times higher than that for alternative bearings (see figure below).



For all MoM implants (any head size) the revision occurrence was much higher than that for the most commonly used 28mm MoP-cemented or hybrid fixation combinations (see figure below).



Uncemented MoM hip implants of any head size had substantially higher revision occurrence when compared to cemented, hybrid or uncemented 28mm MoP devices regardless of age (most common implants used in the UK).

The table below shows this evidence in males. The MoM effect is not modified by age.

Articulation/head size	Year 1	Year 3	Year 5	Year 7
60-year-old males				
Metal-on-metal				
Uncemented 28mm	0.71% (0.52%-0.96%)	1.83% (1.39%-2.39%)	3.18% (2.45%-4.12%)	4.43% (3.34%-5.86%)
Uncemented 36mm	0.83% (0.66%-1.04%)	2.14% (1.80%-2.55%)	3.73% (3.17%-4.38%)	5.18% (4.25%-6.30%)
Uncemented 46mm	1.01% (0.82%-1.24%)	2.61% (2.27%-3.01%)	4.54% (3.97%-5.19%)	6.30% (5.28%-7.51%)
Uncemented 48mm	1.05% (0.85%-1.31%)	2.72% (2.33%-3.18%)	4.72% (4.07%-5.47%)	6.55% (5.43%-7.89%)
Uncemented 50mm	1.10% (0.87%-1.38%)	2.83% (2.38%-3.36%)	4.91% (4.15%-5.80%)	6.81% (5.56%-8.33%)
Uncemented 52mm	1.14% (0.89%-1.46%)	2.95% (2.43%-3.57%)	5.11% (4.23%-6.16%)	7.08% (5.67%-8.82%)
Ceramic-on-ceramic				
Uncemented 28mm	1.19% (0.90%-1.57%)	2.35% (1.85%-2.99%)	3.26% (2.61%-4.06%)	3.88% (3.10%-4.86%)
Uncemented 32mm	1.01% (0.85%-1.21%)	2.00% (1.74%-2.30%)	2.77% (2.42%-3.17%)	3.30% (2.82%-3.88%)
Uncemented 36mm	0.86% (0.72%-1.03%)	1.70% (1.45%-2.00%)	2.36% (1.97%-2.82%)	2.81% (2.28%-3.46%)
Uncemented 40mm	0.73% (0.55%-0.96%)	1.45% (1.10%-1.91%)	2.01% (1.49%-2.70%)	2.39% (1.73%-3.31%)
Metal-on-polyethylene				
Cemented 28mm	0.62% (0.48%-0.80%)	1.20% (0.95%-1.52%)	1.76% (1.40%-2.20%)	2.29% (1.82%-2.88%)
Hybrid 28mm	1.03% (0.75%-1.43%)	1.79% (1.34%-2.37%)	2.60% (1.99%-3.39%)	3.29% (2.51%-4.30%)
Uncemented 28mm	1.17% (0.92%-1.49%)	2.12% (1.73%-2.60%)	2.86% (2.36%-3.47%)	3.42% (2.78%-4.19%)
70-year-old males				
Metal-on-metal				
Uncemented 28mm	0.66% (0.48%-0.90%)	1.70% (1.29%-2.23%)	2.94% (2.25%-3.82%)	4.07% (3.06%-5.40%)
Uncemented 36mm	0.78% (0.61%-0.99%)	1.99% (1.65%-2.40%)	3.44% (2.87%-4.12%)	4.76% (3.85%-5.89%)
Uncemented 46mm	0.95% (0.75%-1.19%)	2.43% (2.04%-2.90%)	4.19% (3.53%-4.97%)	5.79% (4.71%-7.11%)
Uncemented 48mm	0.99% (0.78%-1.26%)	2.53% (2.09%-3.06%)	4.36% (3.62%-5.24%)	6.03% (4.84%-7.48%)
Uncemented 50mm	1.03% (0.80%-1.33%)	2.63% (2.14%-3.23%)	4.54% (3.70%-5.55%)	6.26% (4.96%-7.90%)
Uncemented 52mm	1.07% (0.81%-1.40%)	2.74% (2.18%-3.43%)	4.72% (3.77%-5.89%)	6.51% (5.06%-8.35%)
Ceramic-on-ceramic				
Uncemented 28mm	1.30% (0.96%-1.76%)	2.56% (1.95%-3.35%)	3.53% (2.74%-4.53%)	4.19% (3.24%-5.41%)
Uncemented 32mm	1.10% (0.89%-1.37%)	2.18% (1.81%-2.61%)	3.00% (2.52%-3.58%)	3.57% (2.94%-4.33%)
Uncemented 36mm	0.94% (0.76%-1.15%)	1.85% (1.53%-2.24%)	2.55% (2.08%-3.13%)	3.04% (2.41%-3.82%)
Uncemented 40mm	0.80% (0.60%-1.07%)	1.57% (1.18%-2.10%)	2.17% (1.59%-2.96%)	2.59% (1.85%-3.61%)
Metal-on-polyethylene				
Cemented 28mm	0.55% (0.46%-0.66%)	1.07% (0.93%-1.23%)	1.55% (1.37%-1.76%)	2.00% (1.74%-2.30%)
Hybrid 28mm	0.90% (0.71%-1.15%)	1.55% (1.28%-1.88%)	2.24% (1.88%-2.67%)	2.82% (2.33%-3.40%)
Uncemented 28mm	0.98% (0.80%-1.19%)	1.76% (1.50%-2.06%)	2.37% (2.04%-2.75%)	2.81% (2.38%-3.32%)

Note: results are estimated from multivariable competing risks flexible parametric survival models based on 9,445 uncemented stemmed metal-on-metal cases, 16,136 uncemented ceramic-on-ceramic cases, and for 28mm metal-on-polyethylene: 22,407 cemented, 6,634 hybrid and 9,352 uncemented cases.

Table below shows this evidence in females. The MoM effect is modified by age (younger females seem to have overall higher revision occurrence than older females).

Articulation/head size	Year 1	Year 3	Year 5	Year 7
60-year-old females				
Metal-on-metal				
Uncemented 28mm	0.89% (0.67%-1.18%)	2.45% (1.93%-3.12%)	4.36% (3.46%-5.49%)	6.57% (5.10%-8.43%)
Uncemented 36mm	1.03% (0.85%-1.26%)	2.85% (2.48%-3.26%)	5.06% (4.47%-5.72%)	7.60% (6.44%-8.94%)
Uncemented 42mm	1.16% (0.95%-1.41%)	3.18% (2.78%-3.64%)	5.65% (5.00%-6.37%)	8.47% (7.18%-9.96%)
Uncemented 44mm	1.20% (0.98%-1.48%)	3.30% (2.84%-3.85%)	5.86% (5.09%-6.74%)	8.78% (7.34%-10.48%)
Uncemented 46mm	1.25% (0.99%-1.57%)	3.43% (2.87%-4.09%)	6.08% (5.15%-7.17%)	9.10% (7.45%-11.08%)
Ceramic-on-ceramic				
Uncemented 28mm	0.79% (0.63%-1.00%)	1.71% (1.40%-2.07%)	2.39% (1.98%-2.87%)	3.00% (2.45%-3.68%)
Uncemented 32mm	0.77% (0.66%-0.91%)	1.66% (1.46%-1.88%)	2.32% (2.04%-2.64%)	2.92% (2.46%-3.45%)
Uncemented 36mm	0.75% (0.61%-0.92%)	1.61% (1.34%-1.95%)	2.26% (1.84%-2.77%)	2.84% (2.23%-3.60%)
Metal-on-polyethylene				
Cemented 28mm	0.48% (0.39%-0.59%)	1.09% (0.91%-1.31%)	1.63% (1.36%-1.95%)	2.03% (1.69%-2.44%)
Hybrid 28mm	0.63% (0.47%-0.84%)	1.10% (0.85%-1.42%)	1.62% (1.28%-2.06%)	2.20% (1.72%-2.82%)
Uncemented 28mm	0.83% (0.67%-1.03%)	1.50% (1.24%-1.82%)	1.99% (1.65%-2.40%)	2.31% (1.89%-2.81%)
70-year-old females				
Metal-on-metal				
Uncemented 28mm	0.73% (0.55%-0.97%)	2.01% (1.57%-2.57%)	3.56% (2.80%-4.51%)	5.34% (4.11%-6.91%)
Uncemented 36mm	0.85% (0.69%-1.05%)	2.33% (1.99%-2.72%)	4.13% (3.56%-4.78%)	6.18% (5.14%-7.42%)
Uncemented 42mm	0.95% (0.77%-1.18%)	2.61% (2.22%-3.06%)	4.61% (3.96%-5.37%)	6.90% (5.70%-8.32%)
Uncemented 44mm	0.99% (0.79%-1.24%)	2.71% (2.26%-3.23%)	4.79% (4.03%-5.67%)	7.15% (5.83%-8.76%)
Uncemented 46mm	1.03% (0.80%-1.31%)	2.81% (2.30%-3.43%)	4.97% (4.09%-6.02%)	7.42% (5.93%-9.26%)
Ceramic-on-ceramic				
Uncemented 28mm	0.78% (0.60%-1.01%)	1.66% (1.31%-2.10%)	2.32% (1.85%-2.90%)	2.91% (2.28%-3.69%)
Uncemented 32mm	0.75% (0.62%-0.92%)	1.62% (1.36%-1.92%)	2.26% (1.89%-2.68%)	2.83% (2.30%-3.46%)
Uncemented 36mm	0.73% (0.58%-0.92%)	1.57% (1.27%-1.95%)	2.19% (1.75%-2.75%)	2.75% (2.12%-3.56%)
Metal-on-polyethylene				
Cemented 28mm	0.37% (0.32%-0.43%)	0.85% (0.76%-0.95%)	1.26% (1.14%-1.40%)	1.57% (1.40%-1.76%)
Hybrid 28mm	0.59% (0.47%-0.73%)	1.02% (0.86%-1.21%)	1.49% (1.28%-1.74%)	2.02% (1.69%-2.40%)
Uncemented 28mm	0.81% (0.69%-0.95%)	1.46% (1.28%-1.67%)	1.93% (1.70%-2.19%)	2.23% (1.94%-2.57%)

Note: results are estimated from multivariable competing risks flexible parametric survival models based on 9,234 uncemented stemmed metal-on-metal cases, 19,873 uncemented ceramic-on-ceramic cases, and for 28mm metal-on-polyethylene: 47,162 cemented, 13,383 hybrid and 16,636 uncemented cases.

The table below shows stronger evidence that absolute differences are higher in females when compared to males; women had much higher revision occurrence than men when receiving MoM. Table also shows that within MoM group, larger head size was associated with much higher revision occurrence compared to smaller head size. This was consistent within all age and gender categories.

Age	Head size	Year 1	Year 3	Year 5	Year 7
Males					
55	28mm	0.73% (0.53%-1.01%)	1.89% (1.42%-2.51%)	3.30% (2.50%-4.34%)	4.59% (3.42%-6.16%)
55	36mm	0.86% (0.67%-1.09%)	2.22% (1.83%-2.68%)	3.86% (3.22%-4.63%)	5.38% (4.35%-6.63%)
55	46mm	1.04% (0.84%-1.30%)	2.70% (2.31%-3.16%)	4.70% (4.05%-5.45%)	6.54% (5.42%-7.86%)
55	48mm	1.09% (0.87%-1.36%)	2.81% (2.38%-3.33%)	4.89% (4.17%-5.73%)	6.79% (5.58%-8.25%)
55	50mm	1.13% (0.89%-1.43%)	2.93% (2.44%-3.51%)	5.09% (4.27%-6.06%)	7.06% (5.73%-8.69%)
55	52mm	1.18% (0.92%-1.52%)	3.05% (2.49%-3.72%)	5.29% (4.35%-6.42%)	7.34% (5.86%-9.18%)
60	28mm	0.71% (0.52%-0.96%)	1.83% (1.39%-2.39%)	3.18% (2.45%-4.12%)	4.43% (3.34%-5.86%)
60	36mm	0.83% (0.66%-1.04%)	2.14% (1.80%-2.55%)	3.73% (3.17%-4.38%)	5.18% (4.25%-6.30%)
60	46mm	1.01% (0.82%-1.24%)	2.61% (2.27%-3.01%)	4.54% (3.97%-5.19%)	6.30% (5.28%-7.51%)
60	48mm	1.05% (0.85%-1.31%)	2.72% (2.33%-3.18%)	4.72% (4.07%-5.47%)	6.55% (5.43%-7.89%)
60	50mm	1.10% (0.87%-1.38%)	2.83% (2.38%-3.36%)	4.91% (4.15%-5.80%)	6.81% (5.56%-8.33%)
60	52mm	1.14% (0.89%-1.46%)	2.95% (2.43%-3.57%)	5.11% (4.23%-6.16%)	7.08% (5.67%-8.82%)
70	28mm	0.66% (0.48%-0.90%)	1.70% (1.29%-2.23%)	2.94% (2.25%-3.82%)	4.07% (3.06%-5.40%)
70	36mm	0.78% (0.61%-0.99%)	1.99% (1.65%-2.40%)	3.44% (2.87%-4.12%)	4.76% (3.85%-5.89%)
70	46mm	0.95% (0.75%-1.19%)	2.43% (2.04%-2.90%)	4.19% (3.53%-4.97%)	5.79% (4.71%-7.11%)
70	48mm	0.99% (0.78%-1.26%)	2.53% (2.09%-3.06%)	4.36% (3.62%-5.24%)	6.03% (4.84%-7.48%)
70	50mm	1.03% (0.80%-1.33%)	2.63% (2.14%-3.23%)	4.54% (3.70%-5.55%)	6.26% (4.96%-7.90%)
70	52mm	1.07% (0.81%-1.40%)	2.74% (2.18%-3.43%)	4.72% (3.77%-5.89%)	6.51% (5.06%-8.35%)
Females					
55	28mm	0.98% (0.73%-1.32%)	2.71% (2.09%-3.49%)	4.82% (3.77%-6.14%)	7.25% (5.56%-9.41%)
55	36mm	1.14% (0.92%-1.41%)	3.14% (2.68%-3.68%)	5.58% (4.83%-6.44%)	8.38% (7.01%-9.99%)
55	42mm	1.28% (1.04%-1.57%)	3.51% (3.02%-4.08%)	6.23% (5.42%-7.15%)	9.34% (7.84%-11.10%)
55	44mm	1.33% (1.06%-1.65%)	3.64% (3.08%-4.30%)	6.46% (5.54%-7.53%)	9.68% (8.02%-11.65%)
55	46mm	1.38% (1.09%-1.75%)	3.78% (3.13%-4.56%)	6.70% (5.62%-7.98%)	10.03% (8.16%-12.30%)
60	28mm	0.89% (0.67%-1.18%)	2.45% (1.93%-3.12%)	4.36% (3.46%-5.49%)	6.57% (5.10%-8.43%)
60	36mm	1.03% (0.85%-1.26%)	2.85% (2.48%-3.26%)	5.06% (4.47%-5.72%)	7.60% (6.44%-8.94%)
60	42mm	1.16% (0.95%-1.41%)	3.18% (2.78%-3.64%)	5.65% (5.00%-6.37%)	8.47% (7.18%-9.96%)
60	44mm	1.20% (0.98%-1.48%)	3.30% (2.84%-3.85%)	5.86% (5.09%-6.74%)	8.78% (7.34%-10.48%)
60	46mm	1.25% (0.99%-1.57%)	3.43% (2.87%-4.09%)	6.08% (5.15%-7.17%)	9.10% (7.45%-11.08%)
70	28mm	0.73% (0.55%-0.97%)	2.01% (1.57%-2.57%)	3.56% (2.80%-4.51%)	5.34% (4.11%-6.91%)
70	36mm	0.85% (0.69%-1.05%)	2.33% (1.99%-2.72%)	4.13% (3.56%-4.78%)	6.18% (5.14%-7.42%)
70	42mm	0.95% (0.77%-1.18%)	2.61% (2.22%-3.06%)	4.61% (3.96%-5.37%)	6.90% (5.70%-8.32%)
70	44mm	0.99% (0.79%-1.24%)	2.71% (2.26%-3.23%)	4.79% (4.03%-5.67%)	7.15% (5.83%-8.76%)
70	46mm	1.03% (0.80%-1.31%)	2.81% (2.30%-3.43%)	4.97% (4.09%-6.02%)	7.42% (5.93%-9.26%)

Note: results are estimated from multivariable competing risks flexible parametric survival model based on 9,445 male uncemented stemmed metal-on-metal cases and on 9,234 female uncemented stemmed metal-on-metal cases.

The most current data from the England and Wales National Joint Registry is available in the Smith, 2011 paper (see Appendix L).

Australian National Joint Replacement Registry

The Australian Orthopaedic Association established the National Joint Replacement Registry in 1993, which began data collection in September 1999. All hospitals (both public and private) undertaking joint replacement contribute data to the Registry. The Registry receives information from almost 300 hospitals. As of June 1, 2012, the registry has captured a total of 341,600 hip procedures. The 2011 Annual Report analyzes 294,329 hip replacements from September 1999 - December 31, 2010 including 211,114 primary total hip replacements, 47,835 primary partial hip replacements, and 35,380 revision hip replacements.

The analyses are limited to osteoarthritis and conventional hip replacement only (hip resurfacing is excluded) and adjusted for age and gender. MoM THR (when recalled ASR implant data are included) was associated with between a two to three times higher occurrence of revision when compared to the most common other bearing types (see Table below). Although the rate of revision for MoM THR is always higher than other bearings, the extent varies with time. When comparing MoM THR with Modified MoP THR, using Cox proportional hazards models, the HR is >5 for MoM between 2 and 6 years (see CPR figure and subsequent table detailing HR).

Revision Rates of Primary Total Conventional THR by Bearing Surface (Primary Diagnosis OA)

Bearing Surface	N Revised	N Total	Obs. Years	Revisions/100 Obs. Yrs (95% CI)
Ceramic/Ceramic	1283	43378	183380	0.70 (0.66, 0.74)
Ceramic/Polyethylene	153	2766	19521	0.78 (0.66, 0.92)
Ceramic/Modified Polyethylene	428	17275	62138	0.69 (0.63, 0.76)
Metal/Metal	1617	19330	93020	1.74 (1.65, 1.83)
Metal/Polyethylene	866	16362	108800	0.80 (0.74, 0.85)
Metal/Modified Polyethylene	2374	88749	387561	0.61 (0.59, 0.64)
Ceramicised Metal/Modified Polyethylene	134	8364	28899	0.46 (0.39, 0.55)
Other (5)	60	1122	4050	1.48 (1.13, 1.91)
TOTAL	**6915**	**197346**	**887370**	**0.78 (0.76, 0.80)**

Note: Other includes Ceramic/Metal, Metal/Ceramic, Ceramicised Metal/Polyethylene, Ceramicised Metal/Ceramic and Unknown bearing surfaces.Note: Only Bearing Surfaces with over 500 procedures have been listed.

Note: There are a limited number of legally marketed ceramicised metal on polyethylene designs available in the US, such as an oxidized zirconium.

The 5-year cumulative revision occurrence was 8.8% for MoM THR, between two to three times higher than that for other bearings (table below).

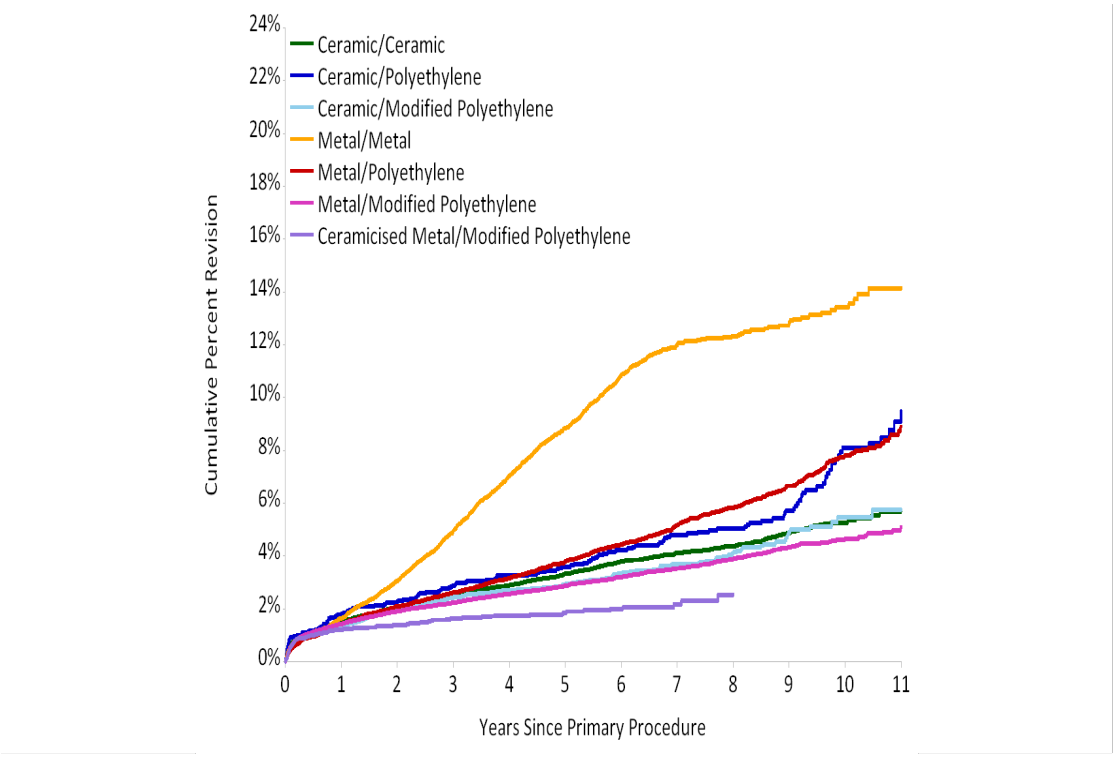
Yearly Cumulative Percent Revision of Primary Total Conventional Hip Replacement by Bearing Surface (Primary Diagnosis OA)

CPR	1 Yr	3 Yrs	5 Yrs	10 Yrs	11 Yrs
Ceramic/Ceramic	1.5 (1.4, 1.6)	2.6 (2.4, 2.7)	3.3 (3.1, 3.5)	5.3 (4.9, 5.7)	5.7 (5.2, 6.3)
Ceramic/Polyethylene	1.8 (1.3, 2.4)	2.9 (2.3, 3.6)	3.6 (2.9, 4.4)	8.1 (6.8, 9.7)	9.5 (7.8, 11.5)
Ceramic/Modified Polyethylene	1.4 (1.2, 1.6)	2.4 (2.2, 2.7)	2.9 (2.6, 3.3)	5.5 (4.6, 6.4)	5.7 (4.8, 6.9)
Metal/Metal	1.6 (1.5, 1.8)	4.9 (4.6, 5.3)	8.8 (8.4, 9.3)	13.4 (12.6, 14.3)	14.1 (13.1, 15.3)
Metal/Polyethylene	1.4 (1.3, 1.6)	2.6 (2.4, 2.9)	3.8 (3.5, 4.1)	7.8 (7.2, 8.4)	8.9 (8.1, 9.8)
Metal/Modified Polyethylene	1.4 (1.3, 1.5)	2.2 (2.1, 2.3)	2.9 (2.7, 3.0)	4.6 (4.4, 4.9)	5.1 (4.7, 5.5)
Ceramicised Metal/Modified Polyethylene	1.2 (1.0, 1.5)	1.6 (1.4, 1.9)	1.9 (1.5, 2.2)		
Other (5)	3.1 (2.2, 4.4)	4.9 (3.7, 6.6)	5.4 (4.0, 7.1)		

Note: Other includes Ceramic/Metal, Metal/Ceramic, Ceramicised Metal/Polyethylene, Ceramicised Metal/Ceramic and Unknown bearing surfaces.

Note: Only Bearing Surfaces with over 500 procedures have been listed.

The figure below depicts cumulative percent revision after primary conventional THR by bearing surface, as discussed above.



The higher risk of revision associated with MoM THR systems is consistent over time up to 7 years post-implantation when compared with modified MoP THR (see below).

Note: These hazard ratios are not finalized. Some time periods violate the proportionality assumption of the Cox Proportional Hazards Model, therefore the results should not be considered as final; however, we anticipate that once the final proportionality has been determined, the hazard ratios will be of a similar value to what is reported here.

Comparison		Hazard Ratio
Metal/Metal vs Metal/Modified Polyethylene	0 - 2Wk:	1.37 (1.05, 1.78), p=0.020
	2Wk - 1.5Yr:	1.35 (1.20, 1.51), p<0.001
	1.5Yr - 2Yr:	3.38 (2.75, 4.16), p<0.001
	2Yr - 4.5Yr:	5.74 (5.18, 6.37), p<0.001
	4.5Yr - 6Yr:	5.46 (4.62, 6.45), p<0.001
	6Yr - 7Yr:	3.72 (2.77, 4.99), p<0.001
	7Yr+:	1.33 (0.93, 1.91), p=0.114

The higher revision rate associated with MoM THR can be better illustrated if MoM THR is compared to all other bearings combined. The revision occurrence for MoM THR is over 2.5 times higher than the average rate for all other bearings combined (see table below).

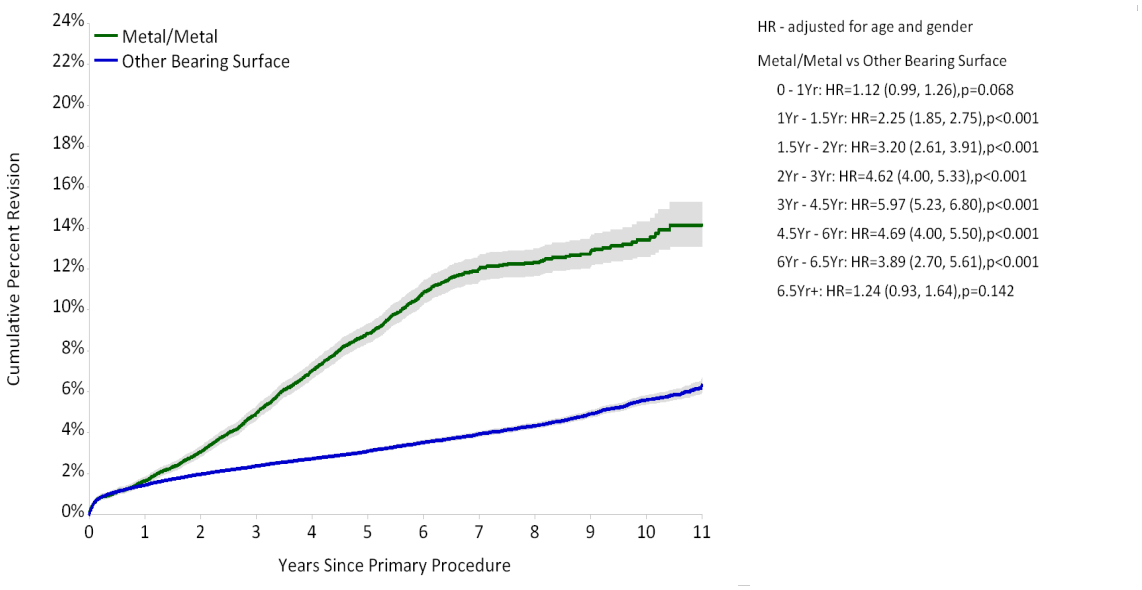
Revision Rates of Primary THR by Bearing Surface (Primary Diagnosis OA)

Bearing Surface	N Revised	N Total	Obs. Years	Revisions/100 Obs. Yrs (95% CI)
Metal/Metal	1617	19330	93020	1.74 (1.65, 1.83)
Other Bearing Surface	5298	178016	794350	0.67 (0.65, 0.69)
TOTAL	**6915**	**197346**	**887370**	**0.78 (0.76, 0.80)**

For example, 5-year cumulative percent revision after MoM THR is 8.8% compared to 3.1% for all other bearing surfaces (see below).

CPR	1 Yr	3 Yrs	5 Yrs	10 Yrs	11 Yrs
Metal/Metal	1.6 (1.5, 1.8)	4.9 (4.6, 5.3)	8.8 (8.4, 9.3)	13.4 (12.6, 14.3)	14.1 (13.1, 15.3)
Other Bearing Surface	1.4 (1.4, 1.5)	2.4 (2.3, 2.4)	3.1 (3.0, 3.2)	5.6 (5.4, 5.8)	6.3 (6.0, 6.7)

The figure below depicts cumulative percent revision after primary THR by MoM and other bearing surfaces (combined).



Note: Shaded area represents the 95% Confidence Interval.

Number at Risk	0 Yr	1 Yrs	3 Yrs	5 Yrs	10 Yrs	11 Yrs
Metal/Metal	19330	18508	14717	8234	648	123
Other Bearing Surface	178016	150896	106530	72908	8603	2220

When ASR implants are excluded from the analyses the absolute difference in revision occurrence between MoM THR and other bearing surfaces is reduced, but the difference is still substantial. MoM THR is associated with between a 30% (MoP) to 70% (modified MoP) higher occurrence of revision.

Revision Rates of Primary Conventional THR by Bearing- Excluding ASR (Primary Diagnosis OA)

Bearing Surface	N Revised	N Total	Obs. Years	Revisions/100 Obs. Yrs (95% CI)
Ceramic/Ceramic	1283	43378	183380	0.70 (0.66, 0.74)
Ceramic/Polyethylene	153	2766	19521	0.78 (0.66, 0.92)
Ceramic/Modified Polyethylene	428	17275	62138	0.69 (0.63, 0.76)
Metal/Metal	796	15352	76452	1.04 (0.97, 1.12)
Metal/Polyethylene	866	16362	108800	0.80 (0.74, 0.85)
Metal/Modified Polyethylene	2374	88749	387561	0.61 (0.59, 0.64)
Ceramicised Metal/Modified Polyethylene	134	8364	28899	0.46 (0.39, 0.55)
Other (5)	59	1121	4047	1.46 (1.11, 1.88)
TOTAL	**6093**	**193367**	**870799**	**0.70 (0.68, 0.72)**

Note: Only Bearing Surfaces with over 500 procedures have been listed.

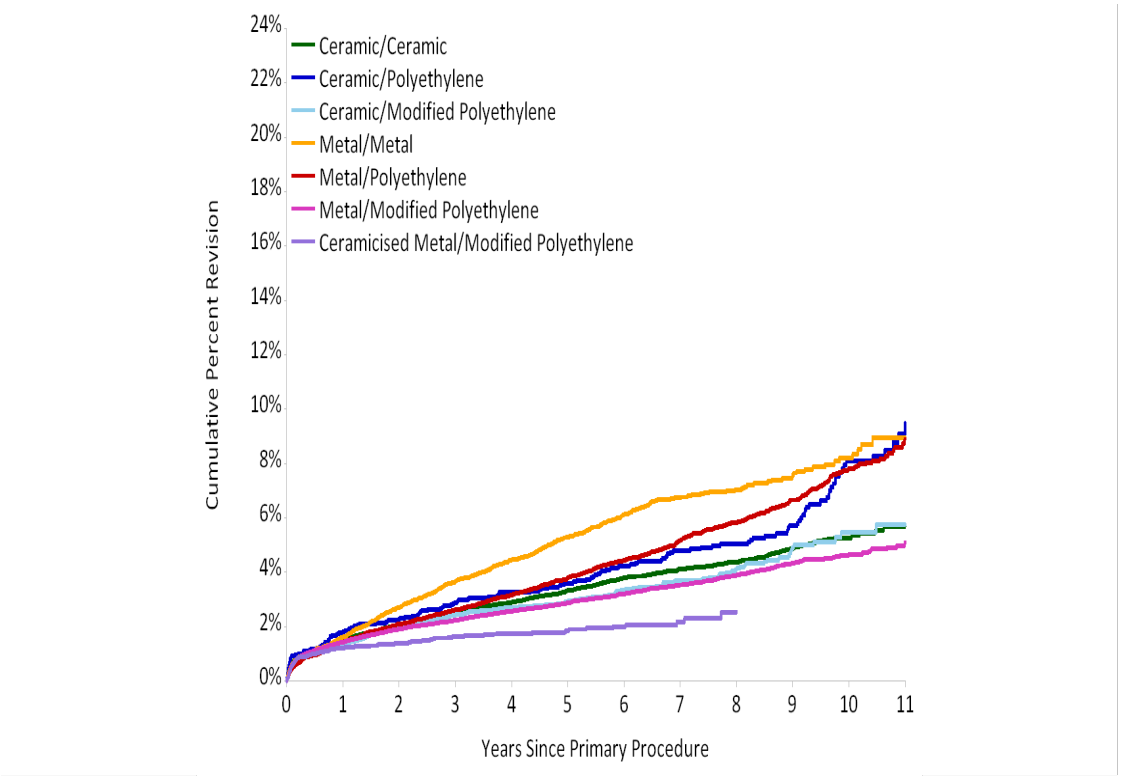
The table and figure below shows that when ASR implants are excluded the 5-year cumulative percent revision occurrence for MoM is 5.3%, which is still substantially higher (as discussed above) when compared to other commonly used alternative bearing surfaces. While the difference is somewhat reduced, at 11 years the MoM THR revision rate is still 80% higher than the most commonly used combination (metal on modified polyethylene combination), though lower than ceramic on polyethylene and comparable to metal on polyethylene. The reduction in the extent of difference in the rates of revision with the longer time points in the Australian registry may be due to the use of a much higher proportion of small head (≤ 32 mm) MoM in the devices that have the longest follow up (after 6 years), relative to devices with shorter follow up time. The longest follow- up of MoM THR in Australia is available for these small head sizes. The comparability of this data to the US population is not well understood as larger head sizes are often implanted and shorter follow-up of MoM THR is available.

Yearly Revision of Primary Conventional THR by Bearing- Excluding ASR (Primary Diagnosis OA)

CPR	1 Yr	3 Yrs	5 Yrs	10 Yrs	11 Yrs
Ceramic/Ceramic	1.5 (1.4, 1.6)	2.6 (2.4, 2.7)	3.3 (3.1, 3.5)	5.3 (4.9, 5.7)	5.7 (5.2, 6.3)
Ceramic/Polyethylene	1.8 (1.3, 2.4)	2.9 (2.3, 3.6)	3.6 (2.9, 4.4)	8.1 (6.8, 9.7)	9.5 (7.8, 11.5)
Ceramic/Modified Polyethylene	1.4 (1.2, 1.6)	2.4 (2.2, 2.7)	2.9 (2.6, 3.3)	5.5 (4.6, 6.4)	5.7 (4.8, 6.9)
Metal/Metal	1.6 (1.4, 1.8)	3.7 (3.4, 4.0)	5.3 (4.9, 5.7)	8.2 (7.5, 9.0)	8.9 (7.9, 10.1)
Metal/Polyethylene	1.4 (1.3, 1.6)	2.6 (2.4, 2.9)	3.8 (3.5, 4.1)	7.8 (7.2, 8.4)	8.9 (8.1, 9.8)
Metal/Modified Polyethylene	1.4 (1.3, 1.5)	2.2 (2.1, 2.3)	2.9 (2.7, 3.0)	4.6 (4.4, 4.9)	5.1 (4.7, 5.5)
Ceramicised Metal/Modified Polyethylene	1.2 (1.0, 1.5)	1.6 (1.4, 1.9)	1.9 (1.5, 2.2)		
Other (5)	3.1 (2.2, 4.4)	4.9 (3.7, 6.6)	5.1 (3.8, 6.9)		

Note: Only Bearing Surfaces with over 500 procedures have been listed.

The Figure below depicts the differences discussed above



Similar to previous analyses, higher revision rates associated with MoM THR can be better illustrated if MoM THR is compared to all other bearings combined for the analyses that exclude ASR implants. The revision occurrence is approximately 70% higher than that for the average rate for all other implants combined (see table below)

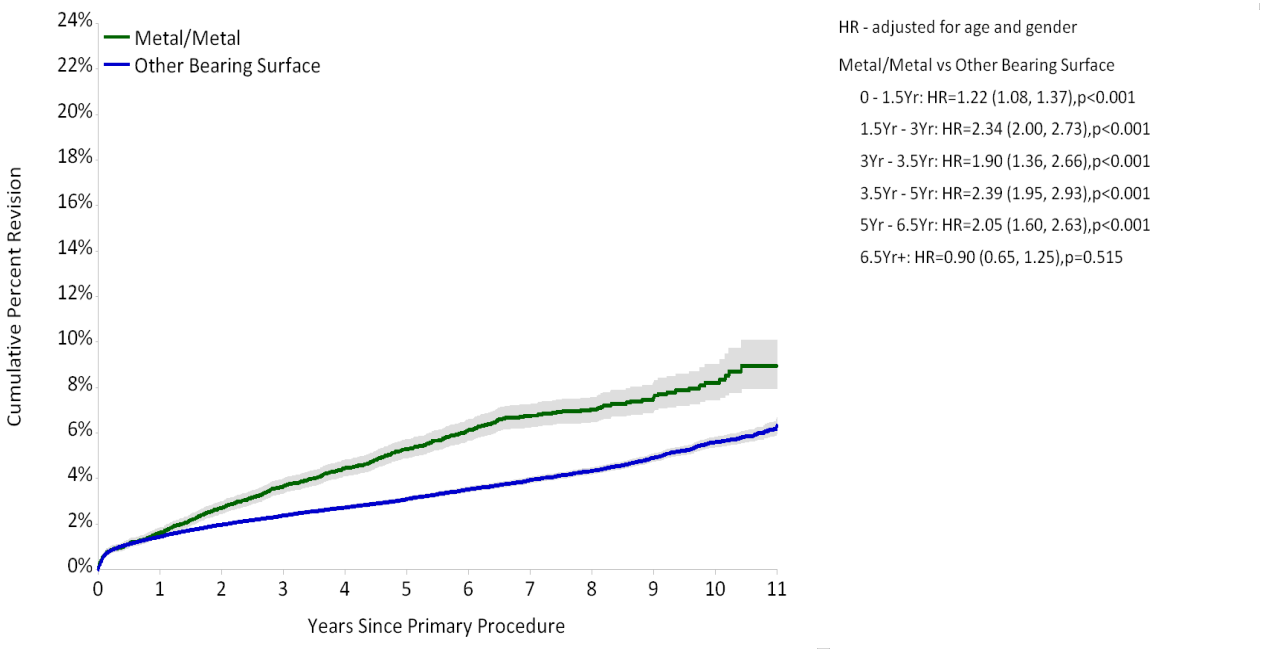
Revision Rates of Primary THR by Bearing Surface - Excluding ASR (Primary Diagnosis OA)

Bearing Surface	N Revised	N Total	Obs. Years	Revisions/100 Obs. Yrs (95% CI)
Metal/Metal	796	15352	76452	1.04 (0.97, 1.12)
Other Bearing Surface	5297	178015	794346	0.67 (0.65, 0.69)
TOTAL	**6093**	**193367**	**870799**	**0.70 (0.68, 0.72)**

For example, cumulative percent revision after MoM THR is 5.3% compared to 3.1% for all other bearings combined at 5-years, or 8.9% vs 6.3% at 11 years (see below). This may also be depicted as a 40% higher risk of revision associated with MoM THR at 11-years.

CPR	1 Yr	3 Yrs	5 Yrs	10 Yrs	11 Yrs
Metal/Metal	1.6 (1.4, 1.8)	3.7 (3.4, 4.0)	5.3 (4.9, 5.7)	8.2 (7.5, 9.0)	8.9 (7.9, 10.1)
Other Bearing Surface	1.4 (1.4, 1.5)	2.4 (2.3, 2.4)	3.1 (3.0, 3.2)	5.6 (5.4, 5.8)	6.3 (6.0, 6.7)

The Figure below depicts the differences discussed above:



Note: Shaded area represents the 95% Confidence Interval.

Number at Risk	0 Yr	1 Yrs	3 Yrs	5 Yrs	10 Yrs	11 Yrs
Metal/Metal	15352	14626	11520	7056	648	123
Other Bearing Surface	178015	150895	106529	72908	8603	2220

The increased MoM failure rates with increased head size and female sex observed in the English and Wales Registry (Smith 2012) have also been reported by the Australian Registry in its Annual reports for the last three years. These differences are the same in that there is an increasing risk of revision for larger head sizes. Where the Australian registry head size data differs is in the 28mm head size group, in which the Australian registry does not show any difference in outcome related to MoM bearing. The reason why this differs from the UK registry may be due to differences in the use of specific MoM THR designs types. The observed increased risk for revision among females with MoM is the same in both registries. This differs from the sex difference observed for other bearings which shows a potentially increased risk of revision for males.

Additional data from this registry is available at:
http://www.dmac.adelaide.edu.au/aoanjrr/publications.jsp?section=reports2011.

New Zealand Joint Registry

The New Zealand Orthopaedic Association established the National Joint Register in 1998, which expanded to include hip surgery in January 2000. All surgical hospitals throughout New Zealand contribute to the registry. Approximately six months following surgery, all registered patients are sent a questionnaire to measure the functional outcome after their surgery in addition to capturing revisions. From January 1, 1999 to December 31, 2010, the registry has captured a total of 81,520 hip procedures, including 71,057 primary hip replacements and 10,463 revision hip replacements.

The data presented consists of unadjusted comparative analyses of MoM THR with alternative bearings excluding resurfacing procedures. Less than 10% of procedures include ASR implants (only 9 out of 111 revisions in the MoM THR group are related to ASR implants). MoM THR was associated with over 40% higher revision occurrence compared to most commonly used MoP bearings, but is only slightly higher than CoP or CoC bearings. The results are statistically significant. If ASR implants were excluded from the analyses, the results are unlikely to change (see below).

Femoral head	Acetab/liner	No Ops	Observed comp. Yrs	Number Revised	Rate/100-component-years	Exact 95% confidence levels	
Ceramic	Ceramic	2595	6835.72	57	0.83	0.63	1.08
Ceramic	Metal	60	29.82	0	0	0	12.37
Ceramic	Polyethylene	7301	27848.25	210	0.75	0.66	0.86
Metal	Metal	3484	12891.17	111	0.86	0.71	1.04
Metal	Polyethylene	37694	163416.65	974	0.60	0.56	0.63
ASR		339	456.18	9	1.97	0.90	3.74

More recent analyses show that most of the revisions in the MoM THR group occur in the >28mm subgroups (due to the large denominator and longer follow up), and the rates of revision are more than two times higher in the >36mm subgroup when compared to 29 to 36mm subgroup (more than 2.5 times higher when compared to 28mm and smaller subgroup).

Similarly, longer follow-up and a larger proportion of revisions are observed in the >36mm MoM subgroup. When compared to any size MoP, the >36 MoM subgroup has a 2.5 times higher rate of revision (see below). While some patients in the >36mm MoM subgroup might include patients with ASR implants, the exclusion of ASR implants is unlikely to affect these results as the rates of revision within the ASR implant group and average >36mm MoM subgroup are comparable (1.97 vs 1.61 revisions per 100 component years).

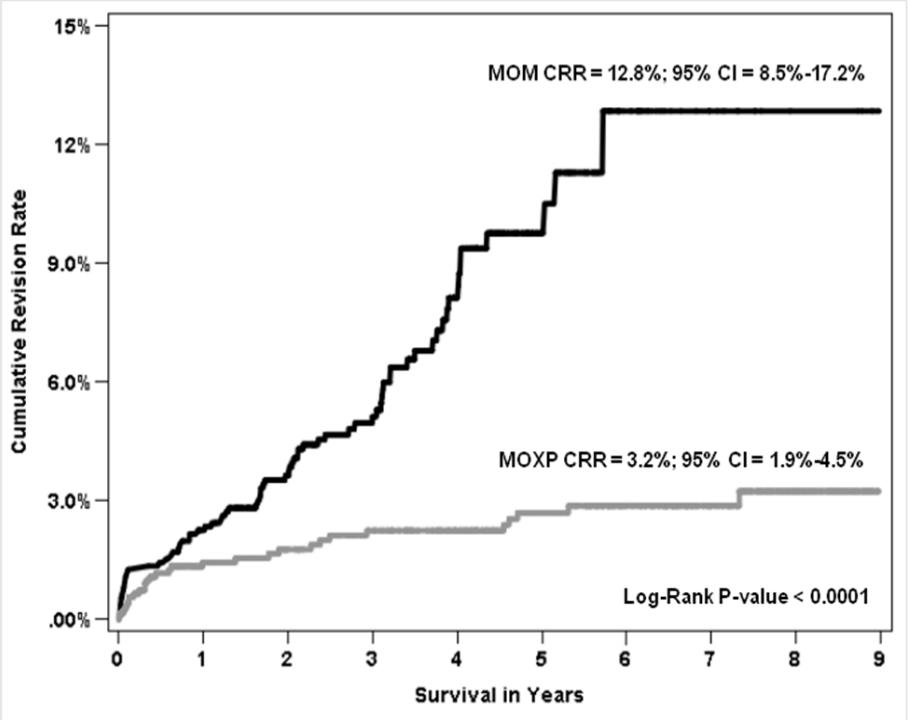
Size	Surfaces	No. Ops.	Observed comp. Yrs	Number Revised	Rate/100-Component years	Exact 95% confidence interval	
<=28	CP	7973	44316	308	0.70	0.62	0.78
<=28	CM	15	20	0	0.00	0.00	18.88
<=28	MM	2765	20010	119	0.59	0.49	0.71
<=28	MP	37076	209531	1354	0.65	0.52	0.59
29_36	CC	4846	14377	106	0.74	0.60	0.89
29_36	CP	2839	5883	46	0.78	0.57	1.04
29_36	CM	335	407	3	0.74	0.15	2.15
29_36	MM	1421	4880	39	0.80	0.57	1.09
29_36	MP	7776	16359	106	0.65	0.53	0.78
>36	CC	250	192	1	0.52	0.01	2.90
>36	CM	6	7	0	0.00	0.00	51.47
>36	MM	1591	5104	82	1.61	1.28	1.99
>36	MP	13	45	0	0.00	0.00	8.13

Additional data from this registry is available at: http://www.cdhb.govt.nz/njr/.

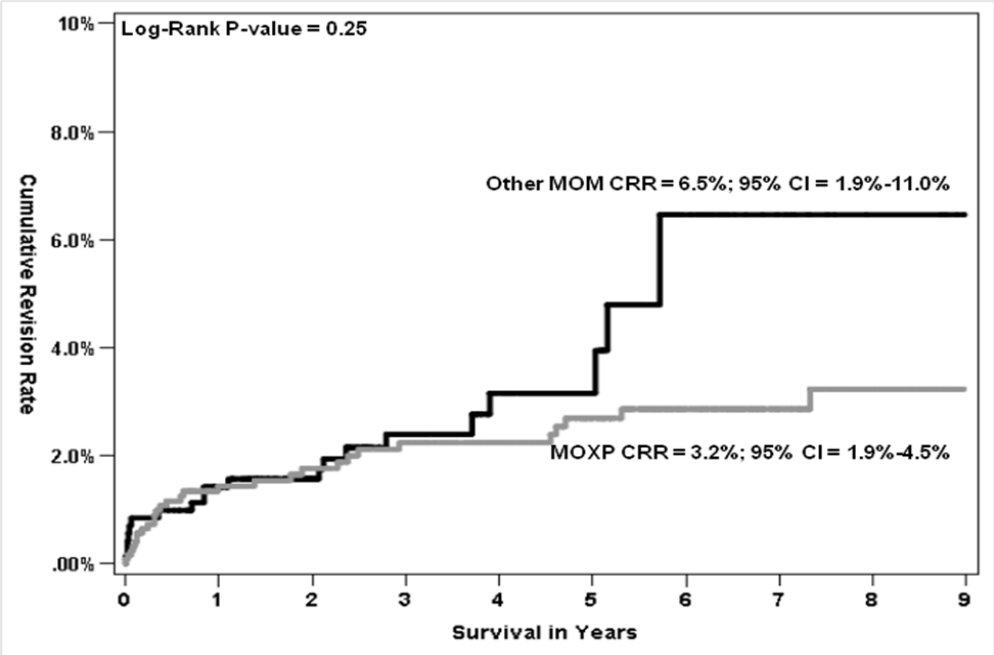
HealthEast Registry (US)

HealthEast Care System established the HealthEast Joint Replacement Registry (HJRR) in 1991, the first community-based joint replacement registry in the U.S. The registry began as a database that allowed tracking of implant use and failure rates among the 90 orthopaedic surgeons performing arthroplasty surgeries in the greater metropolitan area of St. Paul, MN. As of December 31, 2010 the registry has captured 9508 total hip procedures, including 6,146 primary total hip arthroplasties, 2,873 hip hemiarthoplasties, and 489 revision hip arthroplasties.

This analysis includes a matched sample of MoM THR and modified MoP THR patients (excluding resurfacing implants). More than 94% of patients have osteoarthritis. 98% of MoM THR systems had a 36mm or larger head size. In the analyses that include ASR implants, MoM THR was associated with a four times higher occurrence of revision when compared to Metal on cross-linked polyethylene.



When ASR implant patients were excluded there seemed to be a trend towards a higher occurrence of revisions with MoM THR (see below) but the difference was not statistically significant (possibly small sample size and statistical power issues: only 2,404 patients included in the study of which 1,118 patients had MoM THR implants).

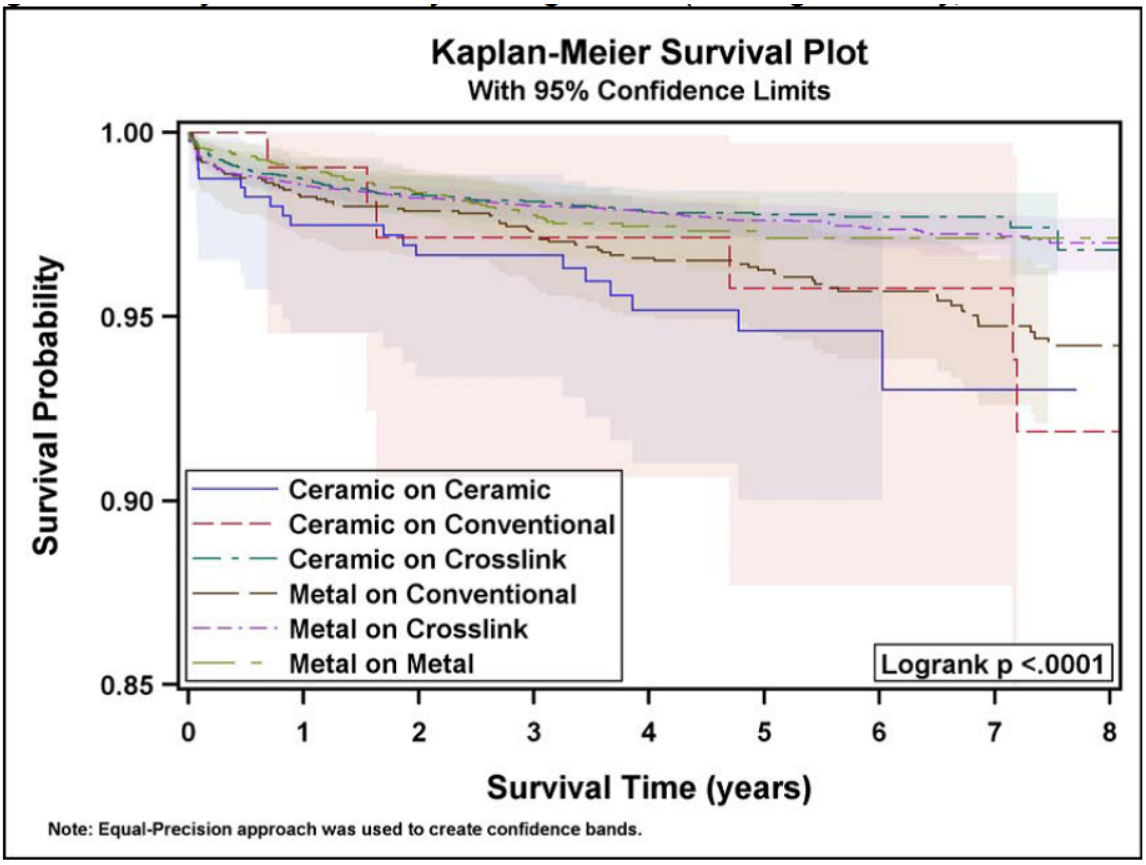


Additional data from this registry is available at: http://www.healtheast.org/orthopaedic-care/joint-replacement-registry.html.

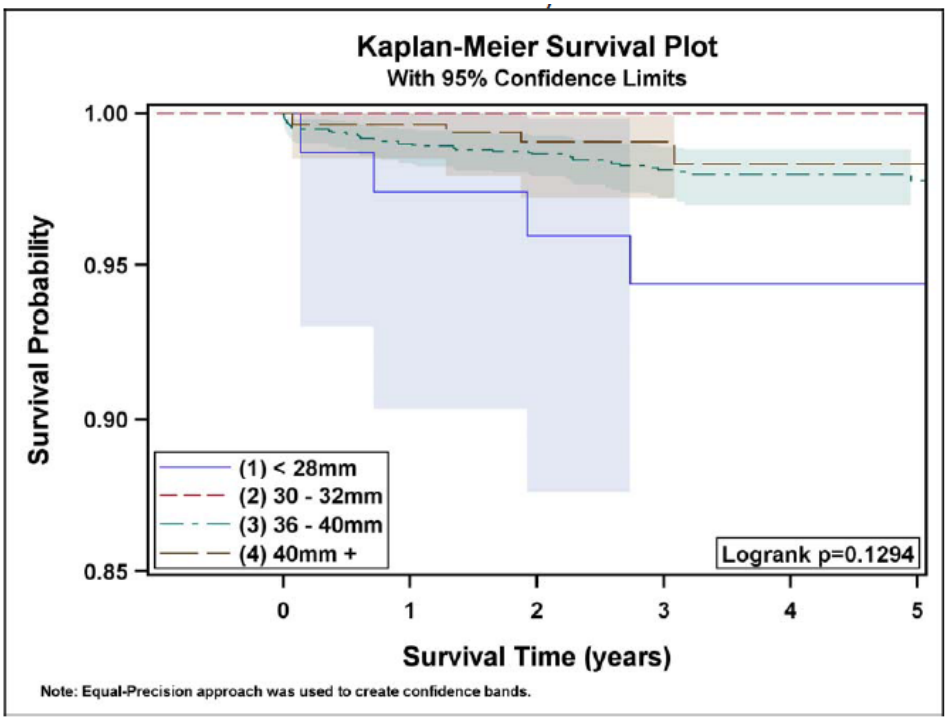
Kaiser Permanente Total Joint Replacement Registry (US)

Kaiser Permanente established the National Total Joint Replacement Registry in 2001 which includes total joint replacement data from April 2001 to March 2008. The Registry contains data from surgeries by more than 350 Kaiser Permanente surgeons nationwide. Registry data are collected prospectively through standardized documentation at the point of care. As of March 31, 2008, there were a total of 24,357 hip procedures, comprised of 21,548 (88.5%) primary and 2,809 (11.5%) revision total hip arthroplasty cases registered.

The unadjusted analysis from this registry includes patients with Osteoarthritis only and excludes resurfacing devices. No differences are found for MoM THR versus other bearing surfaces. The inclusion or exclusion of ASR implants has no impact on the results (see below). However, the revision surgery occurrence for MoM THR is low within the Kaiser Registry (2.9% with ASR implants and 2.2% without ASR implants) and the average follow up is short (as noted by the sharp drops in the lines on the Kaplan-Meier plot).



Within the MoM THR group mostly 28mm and smaller head size subgroups were associated with a substantially higher occurrence of revision when compared to all other head sizes, particularly when ASR implants were excluded (see below). This differs from the recent findings observed in the English and Wales Registry (Smith 2012) where larger head size was associated with higher revision rates.



Additional data for this registry can be found in Paxton, 2012 (see Appendix L).

Registry from Italy (Emilia Romagna)

The Register of Orthopedic Prosthetic Implantology (RIPO) presents hip, knee, and shoulder arthroplasty surgeries carried out in the Emilia-Romagna region, Italy, between January 1, 2000 and December 31, 2010. Altogether data of approximately 98,000 hip, 51,000 knee and 1,100 shoulder prostheses have been reported from 72 Orthopedic Units in 61 Hospitals, either public or private. Data of 97,798 hip prostheses have been reported. Of these, 61,086 (62.5%) were primary total hip arthroplasty surgeries, (24,262) 24.8% were hemiarthroplasty surgeries, and (9,934) 10.2% were total and partial revision surgeries.

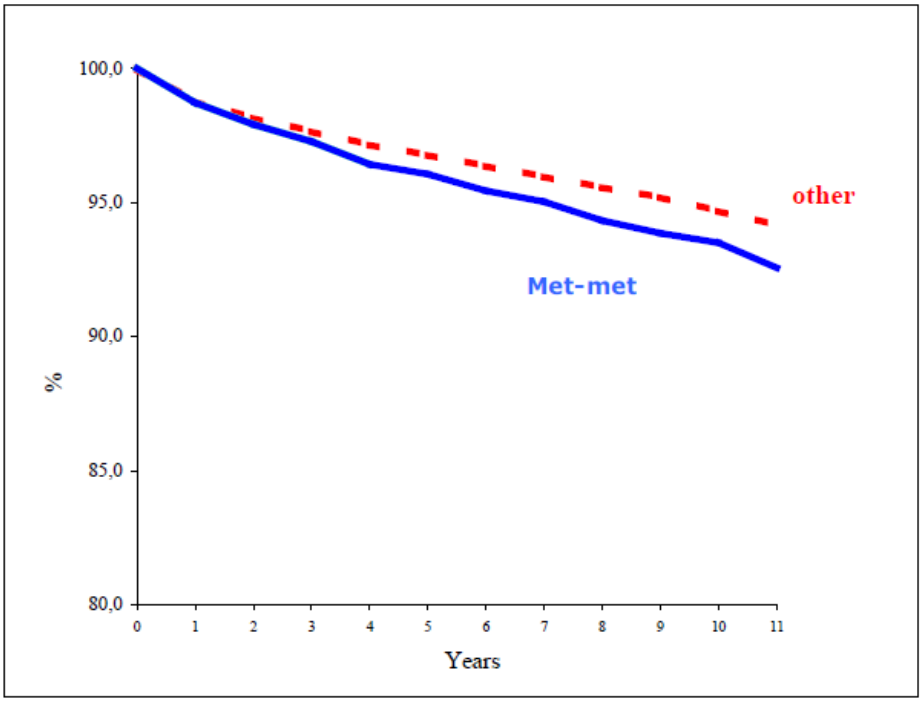
Reported unadjusted data might include hip resurfacing (up to 15% of MoM cases and 2% of the total hips). Other inclusion criteria are also not specified. ASR implant (both THR and resurfacing) use in Italy (Emilia Romagna) is unknown and likely to be very low, if any. Hence the results are likely to represent an ASR excluded sample.

At 11-years of follow-up there was a statistically significant difference in implant survival between MoM hips and other bearings combined. Implant survival was 92.6% in the MoM group and 94.1% in alternative group of all bearings combined (see Figure and tables below). This can also be depicted as 7.4% (MoM) vs 5.9% (alternative) failure rate or 25% higher chance of revision occurrence associated with MoM implants. While the difference between the MoM and all other bearings combined is not as high as within UK and Australian registries, the overall revision occurrence is also slightly lower in the Italian registry which may be related to clinical practice differences (i.e. threshold for surgery) or device differences or patient differences.

Revision Rates of Primary THR by Bearing Surface at 11 Years Post-Implant

Coupling	n. of implants	n. of revisions	% revision
Metal-metal	4.499	182	4.0
Other (all the remaining coupling considered altogether)	44.534	1.462	3.3

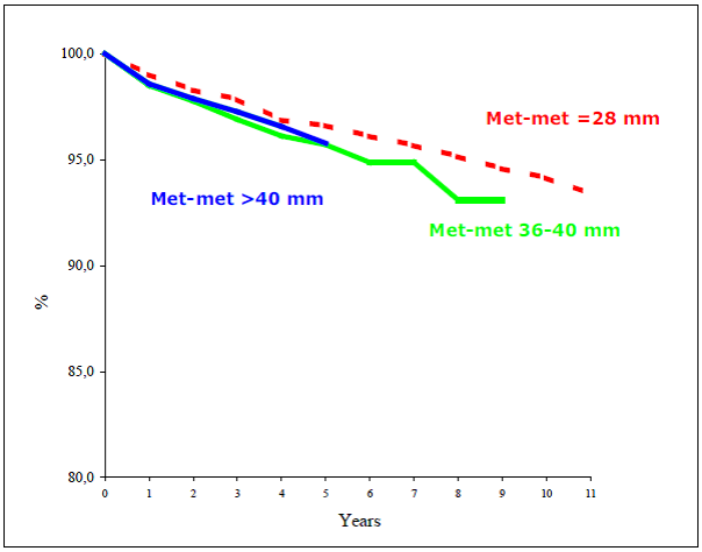
Survival curve all diagnoses all causes for revision.



The table below shows the implant survival discussed above:

Detailed results			
Met-met			
Yrs	**% in site**	**c.i. al 95%**	
0	100,0	100,0	100,0
1	98,7	98,4	99,1
2	97,9	97,5	98,3
3	97,3	96,8	97,8
4	96,4	95,8	97,0
5	96,1	95,4	96,7
6	95,4	94,7	96,2
7	95,0	94,2	95,8
8	94,3	93,4	95,3
9	93,9	92,8	94,9
10	93,5	92,4	94,6
11	92,6	91,0	94,1
Other			
Yrs	**% in site**	**c.i. al 95%**	
0	100,0	100,0	100,0
1	98,8	98,7	98,9
2	98,2	98,0	98,3
3	97,7	97,5	97,8
4	97,1	97,0	97,3
5	96,8	96,6	97,0
6	96,4	96,2	96,6
7	96,0	95,7	96,2
8	95,6	95,3	95,8
9	95,2	94,9	95,5
10	94,7	94,4	95,0
11	94,1	93,8	94,5

Within the MoM hip group, there seems to be a higher occurrence of revisions with 36mm and larger head size implants, but the difference was not statistically significant (possibly small sample size and statistical power issues).



Detailed results

Metal – metal 28 mm			
Yrs	**% in site**	**c.i. al 95%**	
0	100,0	100,0	100,0
1	99,0	98,6	99,5
2	98,3	97,7	98,9
3	97,9	97,2	98,5
4	96,9	96,1	97,7
5	96,6	95,8	97,4

Metal – metal 36-40 mm			
Yrs	**% in site**	**c.i. al 95%**	
0	100,0	100,0	100,0
1	98,5	97,8	99,2
2	97,8	96,9	98,7
3	96,9	95,8	98,0
4	96,1	94,8	97,4
5	95,7	94,3	97,1

Additional data from this registry is available at: https://ripo.cineca.it/Reports.html.

The most recent published annual reports from the registries cited above can be found in Appendix O.