Medicines and Healthcare products Regulatory Agency

Report of the Expert Advisory Group looking at soft tissue reactions associated with metal-on-metal hip replacements.

Chairman: Mr John Skinner

Members:
Professor Paul Gregg
Mr Peter Kay
Mr Martyn Porter
Mr Keith Tucker
Dr Khalid Razak
Mr Andrew Crosbie
Dr Susanne Ludgate

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1. Executive Summary

It is estimated that at least 500,000 current generation metal-on-metal (MoM) hip replacements have been implanted worldwide over the last 15 years with excellent results from experienced surgeons. There are many thousands of patients with these MoM bearings who are functioning at high levels of activity without pain and who are thought to be at low risk of developing problems. However, over the last few years there have been increasing numbers of reports of revisions following unexplained hip pain, sometimes associated with soft tissue reactions which may be severe. An Expert Advisory Group (EAG) involving members of the British Hip Society (BHS), the British Orthopaedic Association (BOA), the Medicines and Healthcare products Regulatory Agency (MHRA), and the National Joint Registry of England and Wales (NJR) was set up to:

- determine the incidence of this problem; and
- advise clinicians on any modifications to current practice which may be necessary to minimise the risk of this adverse reaction and optimise early detection.

Advice for use of MoM hip replacements

The Expert Advisory Group offers the following advice when the use of MoM hip implants is being considered:

(i) Not all components are the same and outcomes may differ.

(ii) Surgeons carrying out MoM hip resurfacing surgery should undergo adequate training and they should have the necessary experience to perform the operation.

(iii) When considering a resurfacing procedure, patient selection is important, with data suggesting that resurfacing performs best in male patients of less than 55 years of age. Resurfacing procedures should be used with caution in those over 65 years of age. Higher failure rates have been reported in females. While there have been successful pregnancies in the first two years following MoM hip replacements, women with MoM hip replacements should be advised to postpone pregnancy for at least two years post hip implantation.

(iv) Patients should be consented thoroughly by the surgeon. The consent process should cover the known risks and potential benefits of MoM hip replacements and specifically the risk of systemic and/or local soft tissue reactions, pain and elevated metal ion levels. Patients should be informed that metal ion levels may be raised for some time after the procedure and that the sequelae of the elevated metal ion levels are currently unknown.

(v) As there is uncertainty with regard to soft tissue reactions and their incidence and effects, all patients with MoM hip bearings should be followed up at least annually for five years post operatively and more frequently in the presence of symptoms. Beyond five years, follow up should be in accordance with locally agreed protocols

(vi) The current role of screening for adverse soft tissue reactions is also unclear. Current evidence suggests that soft tissue reactions are extremely rare in the absence of pain and deteriorating function. Investigations that may be used include blood measurement of cobalt and chromium ions and cross sectional imaging using MARS (Metal Artefact Reduction Sequence) MRI and ultrasound or CT scans.

(vii) It is thought that blood tests to measure cobalt and chromium ions should be performed if:

a) patients have pain or symptoms associated with MoM bearings; or
b) there are radiological features associated with adverse outcomes including component position or small component size; or
c) the patient or surgeon are concerned regarding the MoM bearing; or
d) there is concern about a cohort of patients with higher than expected rates of failure.

(viii) If either metal ion levels are elevated above seven parts per billion (ppb) (119 nmol/L cobalt or 134.5 nmol/L chromium) in whole blood, then a second test should be performed three months after the first in order to identify patients who require closer surveillance, which may include cross sectional imaging

(ix) If imaging reveals soft tissue reactions, fluid collections or tissue masses then consideration should be given to revision surgery.

It is recognised that these recommendations may require modification should new evidence become available

2. Background of events

Clinical studies have shown good results for stemmed/modular MoM hip replacements. Appendix 1 provides background for the use of these devices and some of the relevant clinical data. The England and Wales National Joint Registry (NJR) reported a revision rate for MoM hips, excluding hip resurfacing, of 1.9% over 2003-2008. This was comparable to metal-on-polyethylene (1.6%) and better than ceramic-on-ceramic (2.2%).

Although rare, soft tissue reactions (sometimes described as ALVAL[1] or pseudotumours[2]) can occur in both male and female patients with MoM hip replacements. These reactions have been associated with poor outcomes following revision to conventional total hip arthroplasty (THA)[3]. It appears that a spectrum of MoM soft tissue reactions may exist ranging from fluid collection early on (where revision for pain may give a good outcome) to more extensive necrotic reactions and tissue damage (where revision outcomes are often poor).

One known risk for MoM hip replacements is the potential to release metal wear debris during use. In 2006, at the request of the MHRA, the DH Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment[4] looked at the evidence for genotoxicity from metal wear debris associated with MoM hip replacements. As a result of their deliberations an MHRA Committee on the Safety of Devices Expert Advisory Group assessed the conclusions and clinical implications. For the full report of the Expert Advisory Group see the MHRA website[5] (www.mhra.gov.uk). As this group was drawing up its conclusions, it noted that an increasing number of soft tissue reactions were being reported. In the light of this observation a new Expert Advisory Group (EAG) was established in January 2008 involving members of the BHS, BOA, NJR and the MHRA to assess the significance of soft tissue necrosis associated with MoM hip replacements. This report contains the findings of this new EAG.

3. Remit of the Expert Advisory Group (EAG)

The aim of the Expert Advisory Group was to:

- establish whether the overall revision rate in patients implanted with MoM hip replacements (both total hip replacements and resurfacing devices) could be determined

- establish the percentage of these revisions that involved soft tissue reactions

- identify any modifications to current practice which may be necessary to minimize risk or re-occurrence of failures due to soft tissue reactions

- provide advice to the health service on the future use of MoM hip replacements

- identify any projects which may help to improve our understanding of the spectrum of soft tissue reactions and their frequency of occurrence.

4. Conclusions of the EAG

Peer reviewed publications reporting clinical outcomes for various devices and publications and presentations of soft tissue reactions associated with MoM hip replacements were considered. Information has also been supplied from the London Implant Retrieval Centre (LIRC) and retrieval centres in Stockton-on-Tees and Oxford.

The NJR sent a questionnaire to all surgeons who had revised MoM implants as identified on the NJR database. The study aimed to determine an incidence rate for soft tissue reactions and information on influencing factors for this complication.

In August 2008, when the questionnaires were sent out, there were 551 linked revisions of MoM hip replacements recorded on the NJR database. At that time there were 59,761 MoM hip replacements recorded on the NJR database comprising: 29,768 hip resurfacing arthroplasty (HRA); 11,133 total hip arthroplasties (THA) using large diameter (>36mm) femoral heads and 18,860 THAs using small diameter (<36mm) femoral heads. From the 551 questionnaires sent to orthopaedic surgeons, 352 responses were returned. The findings are discussed below.

4.1. Incidence rate

Soft tissue reactions include a spectrum of descriptions from effusions, inflammatory masses, tissue necrosis to pseudotumour. The returned questionnaires indicated that soft tissue reactions occurred in a small proportion of all revised MoM devices i.e. 50/352 (14.2%). MoM devices can be divided into HRA and THR groups (THR group included resurfacing cups used with extra large modular head requiring the use of a stem or can be metal cup or liner with metal head in a standard cup/head/stem combination). The questionnaire survey returned an incident rate of 15% of the revised HRA devices and 12.5% of the revised THR devices. The reactions occurred in 22 male and 28 female patients. The observed average time to revision for MoM hip replacements with an associated soft tissue reaction was 1.8 years with a range from 23 days to 4.3 years. By 01 March 2009 the NJR linked database had recorded 814 MoM revisions. This would mean that approximately 120 patients may have had a soft tissue reaction associated with their revision. It is likely that the overall incidence of soft tissue reactions is between 1 and 9 per thousand devices implanted.

4.2 Factors affecting occurrences of soft tissue reactions

a) Acetabular cup angle

A wide range of implant angles had been used with the revised devices. In 17/50 (34%) revisions with an associated soft tissue reaction the reports indicated the use of an acetabular cup inclination angle of between 45 and 55 degrees. In the other cases the cup inclination was either outside these angles or not reported. Surgeons will, however, likely have followed the manufacturer's instructions for use when choosing correct cup angle. Sub-optimal cup angles may contribute to the wear and the formation of debris from the implant. A number of MoM device manufacturers have recently highlighted the importance for correct surgical technique and device placement for ensuring a favourable clinical outcome[6,7,8,9]. Early analysis of the London Implant Retrieval Centre (LIRC) data has revealed that approximately one third of failures have a cup inclination angle greater than 50 degrees. Many of these have high blood metal ion levels with soft tissue lesions/fluid collections observed on Metal Artefact Reduction Sequence Magnetic Resonance Imaging scan (MARS-MRI). There is also a group of patients who have well positioned implants but who experience pain severe enough to require implant revision[10]. Characterisation of these patients is essential to ensure against unnecessary revision and to assist in understanding the mechanism of pain generation.

b) Femoral head size

Soft tissue reactions were seen in association with implant femoral head sizes ranging from 28mm to 54mm (with a range of 26-61mm represented). The questionnaire study found there were more females (n=28) than males (n=22) revised with an associated soft tissue reaction. However, other publications have shown that females tend to require smaller hip implant head sizes[11]. MoM hip replacements are sensitive to correct angle of acetabular cup placement and smaller femoral head sizes may be more sensitive to correct angle than larger devices.

c) Metal ion levels

The questionnaire survey indicated that few surgeons requested blood tests for metal ions in patients undergoing revision but, when measured, some had indicated raised blood metal levels. It is difficult, however, to draw conclusions from the questionnaire study alone on the value for metal ion measurements. The LIRC suggests that well functioning MoM implants are associated with very low levels of circulating cobalt and/or chromium ion levels. Although elevated metal ion concentrations are not an indication for revision, it is likely that they will be associated with elevated wear at the interface.

It is accepted that a high inclination angle of the cup increases the chance of edge loading and therefore increases the wear rate of metal-on-polyethylene (MoP) hip replacements[12]. The same is true for MoM hip replacements from retrieval studies[13] and studies that use blood metal ion levels as a surrogate marker for wear rate[14, 15,16.] Both types of bearing produce wear debris that causes adverse biological reactions and therefore are likely to occur more frequently in hips with higher wear rates – although this has not yet been shown conclusively for MoM hip replacements. However, the type of biological reaction depends on the bearing type, with MoP hip replacements being more likely to cause osteolysis[17] and MoM more likely to cause an inflammatory reaction of the hip capsule that has been labelled ALVAL[1] and pseudotumour[2]. Although rare, these soft tissue reactions can be associated with a poor outcomes following revision to conventional THA[18]. However, another series of failed HRA revisions has shown good results[19]. It is possible that these two publications describe revision for different soft tissue entities.

5. Recommendations for further studies

Additional studies may help to improve our understanding of the spectrum of soft tissue reactions and their frequency of occurrence. We recommend the following for further study:

a) Clearer identification of reasons for revision
There is a need for more detailed information gathering to ascertain the reasons for revision of hip resurfacing devices. This may be through the long term follow-up of linked patients on the NJR database.

b) Clearer descriptions for soft tissue reactions
There is a need to develop better terms which can be used to describe the spectrum of soft tissue reactions captured on the NJR database.

c) Further clarification of incidence rate
Users are reporting revisions to both the NJR and to retrieval centres such as the LIRC. It is not clear if the reported revisions to both these organisations overlap or may be separate events. To ensure that all events are captured on the NJR database, a study could be undertaken to link the retrieval specimens from the LIRC, and perhaps other retrieval centres, with the NJR records.

6. Acknowledgements

We would like to thank Professor Jan van der Meulen, Director Clinical Effectiveness Unit, Royal College of Surgeons of England for the advice provided during the course of this study.

7. Appendixes

Appendix 1 - Clinical history of MoM hip replacements

a. Development and use of MoM hip replacements
MoM hip replacements have been in clinical use since 1936. Several generations are recognised but all use both bearing surfaces made from cobalt-chromium-molybdenum alloy[20]. Early devices such as the McKee-Farrar suffered from high friction, sometimes due to equatorial contact or ‘clutch-coning’. However, some survived 30 years of clinical use and showed very little wear[21]. Improvements in manufacturing in the 1990s enabled a revival of this potentially low wearing hip. For the current generation of devices, laboratory studies have shown 100 fold less volumetric wear rates of MoM hip replacements when compared to metal-on-polyethylene (MoP) hips[20,21,22]. This has resulted in more than 500,000 implantations of current generation MoM hip replacements over the last 15 years. MoM bearing surfaces are therefore not new and have been used in some volume over perhaps a 30 year period.

There are reports from inventor-surgeons of the high success rates of these current generation devices[10,23,24,25]. Perhaps more importantly, there are good results reported by non-inventor surgeons (table 1).

Table 1. Clinical outcome reports from non-inventor surgeons of current generation MoM hip resurfacing[8-10]

Study author and date	Implant type	Outcome
Olliviere *et al.* JBJS (Br) 2009[26]	Birmingham Hip Resurfacing	95.8% 5 year survival rate (n=463)
Lilikakis *et al* Orthop Clin North Am 2005[27]	Cormet	97% 2.5 year survival rate (n=70)
Mont *et al* CORR 2005[28]	Conserve Plus	100% 1.5 year survival (n=50)

We estimate that at least 500,000 current generation MoM hips have been implanted and this has been a popular bearing in THA in Europe for many years. Table 2 summarises some of the relevant data. Some of the hip joint registries report the different bearing types (MoM, MoP, and CoC) used but do not distinguish between MoM as a resurfacing or as a modular/stemmed hip replacement.

Table 2. Reports used to estimate the number of implantations of current generation MoM hip replacements implanted over the last 15 years.

Source	Year	Number	Type	Revision rate if available (infection excluded)
Zimmer Metasul brochure[29]	2009	460K total implantations to date	Metasul including Durom	?
Bozic[30]	2009	35% of US hips in 2006 were MoM	All manufacturers	?
NJR, UK[31]	2009	11K with HES linkage since registry began	Resurfacing, all types	5.9% at 3 years
AJR[32]	2009	12K since registry began	Resurfacing, all types	Best = 5% at 8 years Worst = 16% at 7 years
Swedish JR[33]	2007	1K since registry began	Resurfacing, all types	4% at 3 years

Table 2 includes revision rates from the most commonly cited hip replacement registries. Data of this type is usually reported after exclusion of failure due to infection and with osteoarthritis as the primary diagnosis. Satisfactory results have also been reported for other clinical diagnoses including implant survival of 93.2% at 6 years for avascular necrosis, 96.7% at 5 years and 95.2% at 9 years for dysplasia albeit in the series of inventor surgeons.

Therefore, even if all primary and revision operations were recorded and linked, the actual number of revisions is greater than reported. The linking of primary and revision operations can be difficult to validate particularly if the revisions are conducted in the independent sector. However, the UK NJR has linked 157,000 primaries over a 5.5 year period in which approximately 300,000 would have taken place.

b. Factors impacting on revision of MoM hip replacements

Accepting the limitations regarding link ability, there are several patterns shared by these registries. First, the revision rate for MoM hip resurfacing is greater than for all types of hip replacements with a stem, regardless of bearing surface. The two exceptions are that men under 55 years seem to have better implant survival with HRA than THA and the Australian Orthopaedic Association National Joint Replacement Registry (AJR) 2009 report which shows that hip resurfacing has better survival than THA in male patients between 55 and 65 years. It should be noted that some of the revision rates were calculated from a small sample size (sometimes 10 revisions or fewer) and therefore may not be fully representative. Secondly, factors associated with failure include: female gender; small femoral head component size (<50mm); age > 65 years. Female gender and small size are associated so it is not yet clear which the most important contributor to failure is. It is likely that component size (femoral head size less than 50mm) may be more relevant than gender. Preliminary unpublished data from the London Implant Retrieval Centre (LIRC) supports the higher failure rate in females (Figure 1). The effect of age is probably not surprising given that bone quality decreases and that the area of purchase of the femoral component is less for hip resurfacing than for stemmed hip replacement.

Additional risk factors for failure of hip resurfacing are likely to include osteonecrosis, large femoral head cysts, abnormal anatomy, and previous surgery. Finally it appears that not all MoM hips or HRA devices behave the same and it is possible that some devices do significantly better than others[32].

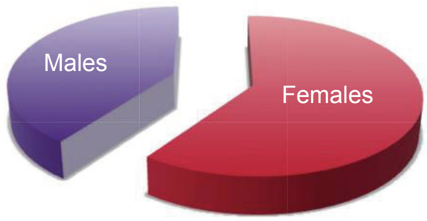

Figure 1. 60% of the 240 MoM hips collected by the LIRC are from females, yet the UK NJR reports that only 33% of hip resurfacings are in females.

c. Hip resurfacing arthroplasty.

Hip resurfacing arthroplasty (HRA) is an operation that can only be performed using MoM components. No other bearing surface allows a relatively thin (3mm) femoral ‘cap’ and acetabular ‘lining’ to provide bone fixation on the non-bearing surface and low wear rates. It was introduced as a technique that preserved femoral neck bone and used larger diameter bearing surfaces. These facts were seen as giving potential advantages in reducing dislocation rates and making revision of the femoral side easier as the index operation did not involve fixation in the femoral canal.

It is clear that in experienced hands excellent results can and have been achieved in centres that have been performing HRA for some time. However, the joint registries show higher failure rates overall when the operation is performed by all surgeons on different populations and this may be for technical surgical reasons or to do with patient selection.

HRA is a technically more demanding procedure than THA. This is due in part to the need to preserve the femoral head and neck and doing this means that it is technically more difficult to accurately locate the acetabular component. More release of soft tissues is required and despite extensive releases it can be difficult to gain exposure in obese patients, heavily muscled patients and patients with abnormal anatomy or high hip offset. The acetabular component is solid and has little capacity for supplementary fixation in patients with normal anatomy although screws can be used with some components in dysplastic anatomy. In soft bone, failure to achieve primary stability may mean that the component moves and reaffixes in a suboptimal position. There is also an incidence of femoral neck fracture with hip resurfacing which, between 1999 and 2003, was 1.46% (0.98% in men and 1.91% in women)[34]. It has reduced over time but at this level was similar to the incidence of dislocation in THA.

In the UK, surgeons rapidly adopted the use of hip resurfacing so that it became the most commonly used type of hip arthroplasty in men less than 50 years old[35]. There has been a slight decline in its use in the last 3 years: 10%, 9% and 7% in the fourth[35], fifth[36] and sixth[31] annual reports of the NJR. This probably reflects a better understanding of which patients to select; males under 65 years of age with good bone appear to do very well from this procedure.

We do not know whether the failure rate of identical MoM bearings is higher when used as a hip resurfacing rather than a stemmed version. Hip resurfacings are more susceptible to femoral neck fracture; however, the rate of this complication has dramatically reduced in recent years and may be equal to the rate of periprosthetic fracture around stemmed hips. The most common cause for revision of a hip resurfacing in the fifth annual report of the NJR was unexplained (‘pain’ plus ‘other’) in 43% of revisions. The proportion of unexplained revisions of stemmed hip replacements was approximately 14%.

There are clinical studies showing good results for stemmed/modular MoM hips[37]. In fact, the UK NJR reported a revision rate for MoM hips (excluding hip resurfacings) of 1.9% over the 2003 – 2008 surveyed periods. This was comparable to MoP at 1.6% and better than CoC at 2.2%. However, the number of MoM primary operations in the survey was only 1,304.

It is therefore likely that some of the early failures of HRA in the registry data are due to failure of fixation or fracture and it is difficult to separate surgical factors from patient factors and these may represent patient selection in the early general cohorts. It is likely that two distinct causes of failure occur: 1) Early: failure of fixation and fracture; 2) Late: unexplained pain some of which are caused by a reaction to metal ions/soft tissue reactions.

d. Soft tissue reactions

The type of biological reaction depends on the bearing type, with MoP more likely to cause osteolysis[17] and MoM more likely to cause an inflammatory reaction of the hip capsule that has been labelled ALVAL [1] and pseudotumour[2]. These findings have been described as soft tissue reactions, and soft tissue necrosis. It is clear that they describe a range of conditions which is a fluid collection or effusion in the majority and may involve necrosis of surrounding tissues. The fluid collections have been described in the joint space, the iliopsoas bursa, the trochanteric bursa and have presented as apparent masses in the groin, buttock or thigh. In the most severe forms there has been extensive necrosis of muscle bone and even nerve. When infection supersedes extensive necrosis, it can be difficult to eradicate. Although rare these soft tissue reactions can be associated with poor outcome following revision to conventional THA. This has been reported in one series[18]. Another series has shown good results after revision for failed HRA[11]. It is possible that these papers describe revision for different entities. In a study of 20 patients with symptomatic metal-on-metal hip arthroplasty, a significant number of these patients presented with early postoperative pain because of an abnormal soft tissue reaction. In these cases MRI scans demonstrated characteristic soft tissue disease where conventional radiographs were frequently normal[38].

Appendix 2

Measuring cobalt and chromium Ions

Chromium and cobalt and other metals present in surgical implants are usually measured by inductively coupled plasma mass spectrometry (ICPMS) using either quadrupole (QICPMS) or high resolution mass spectrometry (HR-ICPMS). Both are capable of accurate analysis, but only HR-ICPMS instruments will allow the measurement of some other metal ions such as titanium and nickel. Electrothermal atomisation atomic absorption spectrometry may also be used, but is less common now in the leading trace element analysis laboratories.

Blood samples for trace element analysis must be collected in trace element free tubes. Tubes are available with either EDTA anticoagulant for the analysis of whole blood samples or with no additive for the analysis of serum samples. There is a small difference in results obtained from whole blood and serum, but both can be used to assess release of metals from implants. The primary advantage of whole blood for the surgeon is that samples can be sent to the laboratory without the need for separation of serum, a step which may allow potential for sample contamination. Some laboratories may advise against the use of stainless steel needles for sample collection, but the amount of contamination introduced via this route is usually low relative to the amount of chromium and cobalt released from high wear joints.

Synovial fluid samples should be collected into the same blood collection tubes or into sterile plastic 'universal' containers. Urine samples should be random collections voided directly into a plastic universal container, although in rare circumstances a timed 24-hour collection may be appropriate. In this case the laboratory should be contacted for advice before sample collection is commenced. In all circumstances glass and metal-containing containers must be avoided.

Trace element assays are available from the Supra-Regional Trace Element laboratories. In all cases the samples must be referred to the analytical laboratory via the local clinical biochemistry laboratory. Most laboratories will be unable to accept referrals from individual surgeons. All laboratories use QICPMS. HR-ICPMS is also available at London (Imperial College).
All laboratories participate in the national QC programme TEQAS, run from the School of Molecular and Biomedical Sciences, University of Surrey. This includes assessment of chromium and cobalt. Most laboratories will also participate in other international EQA schemes.
Metal ion levels have been studied in patients with a metal-on-metal hip implant[10, 39, 40, 41,42,].

The EAG considers 7 parts per billion (ppb) to be a sensible threshold level to use. The LIRC reported cases with cobalt or chromium levels greater than 7ppb as outliers in the group of well-functioning hips. Hart et. al[40] recommended monitoring patients with metal ion levels greater than 7ppb. Some measuring centres prefer to quote concentrations as nmol/L. Conversion from concentration units of ppb to nmol/L can be made by using the following factors:
Cr, atomic mass 51.9961, conversion factor x 19.2
Co atomic weight mass is 58.93332, conversion factor x 17.0

Supra-Regional Trace Element Laboratories

Birmingham
Regional Laboratory for Toxicology
City Hospital NHS Trust
Dudley Road
Birmingham
B18 7QH
Tel: 0121 507 6028
Fax: 0121 507 6021
Deputy Director: Mr T.M.T Sheehan

Glasgow
Scottish Trace Element & Micronutrient Reference Laboratory
Department of Clinical Biochemistry
Royal Infirmary
Glasgow
G4 0SF
Tel: 0141 552 3324
Fax: 0121 211 4288
Deputy Director: Dr A Duncan

Guildford
Trace Element Laboratory
Centre for Clinical Science
School of Biological Sciences
University of Surrey
Guildford
GU2 7XH
Tel: 01483 689978
Fax: 01483 689979
Director: Dr A Taylor
Deputy Director: Dr C Harrinton

Leeds
Leeds Teaching Hospitals NHS Trust
Britannia House
Britannia Road,
Morley
Leeds
LS27 0DQ
Tel: 0113 392 7890 /7852
Fax: 0113 392 7815
Deputy Director: Mr K Newton

London (Imperial College)
Ground Floor Medical Oncology Block
Charing Cross Hospital
Fulham Palace Road
London
W6 8RF
Tel: 020 3311 3644
Fax: 020 3311 1443
Director: Mr B Sampson

London (King's College Hospital)
Trace Metals Laboratory
Department of Clinical Biochemistry
King's College Hospital
Denmark Hill
London
SE5 9RS
Tel: 020 7346 3743
Fax: 020 7737 7434
Deputy Director: Dr K Raja

Southampton
Trace Element Unit
Division of Laboratory Medicine
Southampton University Hospitals NHS Trust
Mail Point 804
Southampton General Hospital
Tremona Road
Southampton
SO16 6YD
Director: Dr V Walker
Tel: 023 8079 6419 (Office), 023 8079 (Laboratory)
Fax: 023 8079 6339

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9. Glossary

AJR	Australian Orthopaedic Association National Joint Replacement Registry
ALVAL	Aseptic lymphocytic vasculitis associated lesion
BHS	British Hip Society
BOA	British Orthopaedic Association
EDTA	Ethylenediaminetetraacetic acid
EQA	External Quality Assurance
Co	Cobalt
CoC	Ceramic-on-ceramic
COM	Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment
Cr	Chromium
CSD	Committee on Safety of Devices
DH	Department of Health
HRA	Hip resurfacing arthroplasty
HR-ICPMS	High resolution mass spectrometry
ICPMS	Inductively coupled plasma mass spectrometry
JR	Joint registry
LIRC	London Implant Retrieval Centre
MARS	Metal Artefact Reduction Sequence
MHRA	Medicines and Healthcare products Regulatory Agency
MoM	Metal-on-metal
MoP	Metal-on-polyethylene
MRI	Magnetic resonance imaging
NJR	National Joint Registry of England and Wales
ppb	part per billion
QC	Quality control
QICPMS	Quadrupole inductively coupled plasma mass spectrometry
TEQAS	Trace Elements External Quality Assessment Scheme
THA	Total hip arthroplasty