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Title: Follow-up of metal-on-metal hip replacement patients is currently not evidence based or cost effective

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**Cover letter**

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Title: Follow-up of metal-on-metal hip replacement patients is currently not evidence based or cost effective

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IRB approval: The work presented did not require IRB approval as this is a review article.

All of the aforementioned authors have actively participated in the study, and the work has not been submitted elsewhere for consideration for publication.

**Response to Reviewers Comments for Manuscript # JOA-D-14-001164 "Follow-up of metal-on-metal hip replacement patients is currently not evidence based or cost effective"**

**19<sup>th</sup> February 2015**

Reviewer #1: The authors have reviewed the current recommendations on the follow up of MOM THRs. This is a timely topic that will be of interest to the readership. The article is very long and needs to be shortened.

**We have significantly shortened the paper (initially 4229 words and now 3365 words which is a 20% reduction). We feel this is an acceptable reduction given we have had to make additions to the paper to respond to both reviewers' comments. We feel any further shortening will significantly affect the content of the paper, given it needs to include a comprehensive review of the current literature as well as the financial analysis.**

Specific comments:

Line 30; not always "large"

**We have removed reference to "large amounts" of metal debris from this sentence as suggested (page 2, paragraph 1, line 30).**

Line 35: "short term outcomes are poor"? Not always

**We have modified this sentence to "short-term outcomes following revision are often poor." (page 2, paragraph 1, lines 34-35). We understand some series have shown better results than others, but a recent systematic review on this topic (Matharu GS et al. Revision of metal-on-metal hip replacements and resurfacings for adverse reaction to metal debris: a systematic review of outcomes. *Hip International* 2014; 24: 311-320) demonstrated the majority of series report sub-optimal/poor short-term outcomes following ARMD revision.**

Line 139: this doesnt make sense- closer follow up for devices with better track records?

**We apologise for our original wording, and have now made this point clearer (page 6, paragraph 3, line 138-141).**

Line 155: define significant

**We have reworded this sentence and have provided some figures from national data (page 7, paragraph 1, lines 151-152).**

Line 160-161: several have not

**We have reworded this sentence to reflect this (page 7, paragraph 2, line 156-158).**

Line 240: a comment on the return of levels following revision is helpful to include

**This has now been discussed with two references added (page 10, paragraph 2, lines 236-238).**

Line 258: what disease?

**This comment has been removed and reworded for clarity (page 10, paragraph 4, line 248-249).**

Reviewer #2: This is a well written comprehensive review of the current variations in worldwide guidance on follow-up of metal-on-metal hip arthroplasty and this authors should be congratulated on this.

**No specific comments to address.**

They present a concise summary of the variations between protocols under each sub-heading, highlighting relevant literature to support/refute the suitability of the protocol in accordance with current evidence.

**No specific comments to address.**

Although it is difficult to estimate an accurate cost analysis, the authors have summarised and presented in their table a comparative analysis which can be interpreted easily.

**No specific comments to address.**

The authors acknowledge that further research should be done and analysis is required to improve the understanding of the natural history of ARMD and to evaluate the most appropriate and cost effective monitoring.

**No specific comments to address.**

It would be useful in their conclusion to collate their interpretation of the merits and pitfalls of each of the protocols in accordance with the evidence quoted from the current literature to suggest, at least in the interim period whilst further research is carried out, their perceived ideal follow-up protocol as an updated guideline.

**We have now actioned this request (page 16, paragraph 1, lines 376-378). However because reviewer 1 wished us to reduce the length of the manuscript, we have included the recommendations in a Table (Table 4) rather than within the text.**

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18<sup>th</sup> February 2015

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**Follow-up of metal-on-metal hip replacement patients is currently not evidence based or  
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**Follow-up of metal-on-metal hip replacement patients is currently not evidence based or cost effective**

**Abstract**

Over one-million patients worldwide have received metal-on-metal (MoM) hip replacements with a significant proportion requiring revision surgery in the short-term for adverse reaction to metal debris (ARMD). Worldwide authorities have subsequently issued follow-up guidance for MoM hip patients. This article compares follow-up guidelines for MoM hips published by five worldwide authorities, analyses these protocols in relation to published evidence, and assesses the financial implications of these guidelines. A number of major differences exist between authorities regarding patient follow-up, with vast cost differences between protocols (£84 to £988/patient/year for stemmed MoM hips and £0 to £988/patient/year for hip resurfacing). Current worldwide guidance is neither evidence-based nor financially sustainable with most protocols lacking the sensitivity to detect asymptomatic ARMD lesions.

*Word count* = 118

**Keywords**

metal-on-metal; hip resurfacing; total hip replacement; follow-up; finance; guidelines

**Follow-up of metal-on-metal hip replacement patients is currently not evidence based or cost effective**

#### **Abstract**

Over one-million patients worldwide have received metal-on-metal (MoM) hip replacements with a significant proportion requiring revision surgery in the short-term for adverse reaction to metal debris (ARMD). Worldwide authorities have subsequently issued follow-up guidance for MoM hip patients. This article compares follow-up guidelines for MoM hips published by five worldwide authorities, analyses these protocols in relation to published evidence, and assesses the financial implications of these guidelines. A number of major differences exist between authorities regarding patient follow-up, with vast cost differences between protocols (£84 to £988/patient/year for stemmed MoM hips and £0 to £988/patient/year for hip resurfacing). Current worldwide guidance is neither evidence-based nor financially sustainable with most protocols lacking the sensitivity to detect asymptomatic ARMD lesions.

## Introduction

Over one-million patients worldwide have received large-diameter metal-on-metal (MoM) hip replacements (hip resurfacing (HR) and total hip replacement (THR)) [1]. Recently high short-term failure rates due to adverse reaction to metal debris (ARMD) have been observed with MoM hips [2-6]. ARMD is the sequelae of metal debris released from MoM articulations due to wear and corrosion [7], which can result in destructive soft-tissue masses often requiring revision [8]. In the United Kingdom (UK) the prevalence of ARMD revision surgery is increasing, accounting for 13% of all revisions performed in 2012 [9]. As ARMD can cause significant bone loss and muscle damage, short-term outcomes following revision are often poor [10,11]. These unsatisfactory outcomes are concerning given most patients are young and active [12-14]. Early revision surgery for ARMD is currently recommended which may improve outcomes [15,16]. To identify patients with ARMD early, regulatory authorities worldwide have published follow-up guidance for MoM hip patients [16-20].

This article compares follow-up guidelines for MoM hip patients issued by five worldwide authorities, analyses these protocols in relation to published evidence, and assesses the financial implications.

## **Follow-up guidelines**

Guidance for MoM hip follow-up has been issued by the: UK Medical and Healthcare products Regulatory Agency (MHRA) [16], European Federation of National Associations of Orthopaedics and Traumatology (EFORT) [17], United States of America (USA) Food and Drug Administration (FDA) [18], Therapeutic Goods Administration of Australia [19], and Health Canada [20] (Table 1). Major differences in follow-up guidance exist between authorities.

### **• HR and THR**

The USA and Canadian authorities do not distinguish between the follow-up of HRs and THRs. Other authorities make this distinction and follow-up large-diameter ( $\geq 36\text{mm}$ ) THRs regardless of symptoms [16,17,19]. Furthermore, these three authorities stratify HR follow-up by symptoms, with some also using ARMD risk factors. Small HR femoral head sizes are a high-risk group requiring at least annual surveillance in European ( $<50\text{mm}$ ) and Australian ( $\leq 45\text{mm}$ ) guidance, but not by the MHRA. Although USA and Canadian guidance stratifies follow-up according to symptoms, both advise closer follow-up (review intervals not stated) for patients with ARMD risk factors.

### **• Follow-up regularity**

Only the FDA advocate universal follow-up for all MoM hips for the implant lifetime (six-monthly reviews if symptomatic, and 1-2 yearly if asymptomatic). All other authorities recommend at least annual follow-up for most MoM hips, including large-diameter THRs, HRs with ARMD risk factors, and all symptomatic patients. Asymptomatic HR patients and those without ARMD risk factors are either reviewed according to local protocol or annually for five-years followed by local protocol.

76

77 • **Investigations**

78 All authorities stratify investigations according to patient symptoms. Symptoms are defined  
79 by three authorities as pain and abnormal gait (including limping) [16,18,20], whilst  
80 European and Australian guidance do not define symptoms. The FDA and Canadian guidance  
81 further define symptoms as noises from the hip, decreased range of motion, swelling, local  
82 nerve palsy, and dislocation. Although patient reported outcome measures such as the Oxford  
83 Hip Score [21] are reliable and responsive instruments, no guidance recommends their usage  
84 during follow-up.

85

86 For symptomatic patients blood metal ions and cross-sectional imaging is universally  
87 recommended. For asymptomatic patients recommendations include: clinical review only  
88 [18,20], radiographs with metal ions [17], metal ions alone for THRs [16], and radiographs,  
89 metal ions, and cross-sectional imaging for all THRs and HRs with small head sizes [19].

90

91 All authorities recommend whole blood for determining metal ion concentrations, with serum  
92 also acceptable in Australia and Canada. European guidance requires measurement of cobalt  
93 only, though all other authorities recommend both cobalt and chromium sampling.

94

95 The MHRA make no recommendations regarding hip radiographs, whilst the FDA and  
96 Canada suggest radiographs in symptomatic patients only. All authorities advocate either  
97 metal artefact reduction sequence magnetic resonance imaging (MARS MRI) or ultrasound  
98 for cross-sectional imaging, however both the FDA and European guidance consider  
99 computed tomography (CT) to also be acceptable.

101     •     **Blood metal ion thresholds**

102     Blood metal ion concentrations above 7µg/l are of concern in two authorities [16,20] with the  
103     MHRA recommending repeat testing within three-months of abnormal results. European  
104     guidance suggests asymptomatic patients with concentrations between 2µg/l-7µg/l require  
105     cross-sectional imaging. No metal ion thresholds for concern are recommended by the other  
106     two authorities [18,19].

107  
108     •     **Thresholds for revision**

109     All authorities suggest revision surgery is considered in patients with abnormal cross-  
110     sectional imaging and/or rising blood metal ions. European guidance suggests blood cobalt  
111     above 20µg/l is an indication for revision.



In light of these major differences in follow-up guidance between authorities the best available evidence will now be considered.

#### **Do all patients require follow-up?**

All MoM hips are theoretically at risk of ARMD. It is clear implants with high failure rates need regular follow-up. This includes all large-diameter MoM THRs given their significantly higher failure rates compared to other articulations, [5]. Follow-up for HR patients is less clear.

Similar follow-up protocols for THRs should be used for HR designs with poor outcomes, with MHRA guidance reflecting this for the Articular Surface Replacement (ASR) HR. The Birmingham Hip Resurfacing (BHR) is the most frequently implanted HR device worldwide [22]. The BHR has established 10-15 year outcomes when implanted by designing [14,23] and independent surgeons [12,13,24], and is also supported by registry data [9,25]. Therefore, for proven HR implants, such as the BHR, closer follow-up is recommended in those with ARMD risk factors [26-28], whilst less regular follow-up is required for patients with established devices but without these risk factors.

It is somewhat concerning that FDA and Canadian guidance fails to separate follow-up protocols for THRs and HRs. In contrast, European and Australian guidance risk stratifies HRs by patient and implant factors, which is advisable given current evidence.

#### **Should symptoms decide follow-up?**

Although all authorities stratify follow-up according to symptoms, asymptomatic ARMD lesions have been observed in up to 61% of MoM hips [29-31]. This approach will result in

ARMD being undetected in asymptomatic patients. In particular, FDA and Canada allocate limited resources for asymptomatic THR patients who are known to be at risk of implant failure (6.2% five-year failure rate for MoM THRs compared to 1.6% for other articulations) [5].

### **Role of blood metal ions**

Blood metal ions are a surrogate marker of in-vivo MoM bearing wear [32]. Some studies have demonstrated raised blood metal ion concentrations are associated with MoM hip failure [33-36].

Although both whole blood and serum metal ions are acceptable investigations, important differences exist between sample types. Serum cobalt and chromium are up to 1.4 times greater than their respective values in whole blood, with stronger correlation of cobalt in serum and whole blood compared to that of chromium [37,38]. Consistently using the same sample type is therefore important, and is recognised by authorities allowing whole blood or serum sampling [19,20].

Analytical methods are equally important, with one study observing clinically significant differences in whole blood metal ion samples from the same patients analysed at two laboratories [39]. The UK monitors accredited laboratories performing metal ion analysis, with evidence that results are accurate and reproducible between centres [40]. Variable information is provided by all authorities regarding metal ion analysis, though most recommend serial samples are sent to the same laboratory.

In MoM hip patients, blood metal ion concentrations above 7µg/l are a cause for concern by some authorities [16,20]. This threshold had good specificity (89%) but poor sensitivity (52%) for detecting failed MoM hips in one study, with the optimal threshold identified as a cobalt or chromium of 4.97µg/l (86% specificity and 63% sensitivity) [41]. Similar thresholds for poorly functioning HRs have been proposed by Van Der Straeten *et al.* (cobalt 4.0µg/l and chromium 4.6µg/l) [35] and Sidaginamale *et al.* (cobalt 4.5µg/l) [42] with all cut-offs having higher specificity than sensitivity.

Few studies have assessed blood metal ion thresholds in MoM THRs. In a cohort including 190 unilateral THRs, 7µg/l had low sensitivity (57%) and specificity (65%) for identifying ARMD [43]. Sensitivity (86%) improved with a threshold of 3.5µg/l but specificity was low (27%) [43]. Another study of 597 ASR hips observed different diagnostic test characteristics for blood metal ions in HRs and THRs [36]. Cobalt was raised out of proportion to chromium in failed THRs, suggesting a different mechanism for ion generation [36]. This is most likely related to metal debris generated from taper and modular junctions, rather than the bearing [44]. Only one study has devised cut-offs for poorly functioning bilateral HRs (cobalt 5.0µg/l and chromium 7.4µg/l) [35]. However these thresholds have not been validated and may not apply to bilateral MoM THRs.

Although no single blood metal ion threshold will reliably identify all ARMD patients, the 7µg/l cut-off recommended by some is too high. Evidence suggests the threshold for unilateral MoM hips should be below 5.0µg/l. European guidance recognises the threshold should be between 2µg/l-7µg/l with the exact level still to be determined.

## **Role of cross-sectional imaging**

Numerous studies have demonstrated both ultrasound and MARS MRI are acceptable for identifying ARMD in MoM hips [29,30,43,45-47]. All authorities recommend using either modality with no preference stated. These recommendations are appropriate as presently no consensus exists regarding which modality is most effective for identifying ARMD or monitoring progression [48], with the relative merits of each previously described [49].

Few studies have compared ultrasound against MARS MRI for assessing MoM hips [48-50]. Studies by Garbuz *et al.* (n=40) [48] and Nishii *et al.* (n=64) [50] demonstrated ultrasound was an effective screening tool for identifying ARMD. Garbuz *et al.* concluded that a negative ultrasound excludes ARMD, as ultrasound was 100% sensitive [48]. In contrast, a smaller study (n=19) observed ultrasound was inferior to MRI for detecting ARMD lesions and muscle atrophy [49]. Furthermore a recent consensus statement suggested MRI will have an increasing role in clinical decision making [51]. However, delays of up to one-year occurred between performing ultrasound and MRI in some patients [49,50]. In addition, none of these studies formally compared imaging findings to the true gold standard of findings at revision [48-50]. Analysis of 167 MoM hips revised for ARMD demonstrated good sensitivity (71%) and specificity (87%) of MRI for detecting intra-operative ARMD lesions [52], though such an assessment has not been performed with ultrasound.

CT scanning provides details regarding implant position and bony defects [53,54]. However recent observations suggest CT is unsuitable for routine MoM hip imaging [55]. Therefore the FDA and European guidance should not recommend CT for first-line imaging.

## **When should follow-up be repeated?**

Decisions regarding follow-up regularity require well-designed longitudinal cohort studies with patients undergoing repeated assessments. Although the natural history of ARMD remains incompletely understood [56], more recent studies have assessed the utility of repeating blood metal ions and cross-sectional imaging in MoM hips.

### **• Repeat blood metal ions**

After repeating blood metal ions at one-year in 254 unilateral ASR patients Reito *et al.* observed most HRs had concentrations below published thresholds [35] on both tests, whilst 32% of THRs with normal initial cobalt had raised levels on repeat testing [57]. In another study repeating blood metal ions at a mean of 27 months in 205 patients with mainly high-risk ASR HRs, no significant difference in cobalt concentration was demonstrated with time since HR [34]. Two studies repeating blood metal ions following revision both observed most patients have significantly decreased or normal concentrations three-months after bearing exchange, though chromium decreases at a slower rate than cobalt [58,59].

Repeating blood metal ions in THRs may therefore be useful but no more regularly than annually. In HRs with low metal ion levels, repeated testing appears unnecessary without clinical changes. HR patients with raised levels should undergo repeat testing as described for THRs. Repeating blood metal ions within three-months for patients with high initial levels as recommended by some authorities [16,19] appears unnecessary.

### **• Repeat cross-sectional imaging**

Two studies have used serial MRI to assess MoM hips [60,61]. Repeat imaging in 103 MoM THRs demonstrated 9.5% of patients with normal initial MRIs developed ARMD, though this

occurred over several years [60]. Similarly, little variation was observed in 37 asymptomatic HRs when MRIs were repeated within one-year [61].

Two further studies assessed the natural history of ARMD using serial imaging. Repeat ultrasound in 20 asymptomatic patients with ARMD demonstrated most lesions increased in size in the short-term with occasional remission of small masses [56]. Similar results were observed in 24 asymptomatic MoM hips with ARMD undergoing repeat MRI, with larger lesions most likely to increase in size [62].

Repeat cross-sectional imaging in ARMD patients should not be performed more frequently than annually. This is supported by findings that MRI scans performed less than three-months, between six-months and twelve-months, and over one-year before revision surgery had respective sensitivities of 88%, 77%, and 29% for detecting intra-operative ARMD [52]. The costly recommended FDA follow-up for symptomatic MoM hips (six-monthly including repeat cross-sectional imaging) is therefore not justified.

Furthermore, it is unclear whether patients with normal blood metal ions and imaging can be safely discharged, or whether they need repeat investigations after an interval. Serial MRI studies [60,61] suggest patients with normal initial imaging do not need repeat imaging in the short-term. However longer-term studies with repeat investigations in these patients are needed to determine the natural history of ARMD and follow-up required.

#### **What is the threshold for revision?**

Poor short-term outcomes have been reported following ARMD revision [10,11] with few studies assessing prognostic factors of outcomes post-revision [53,63,64]. One study

274 attributed improved outcomes following ARMD revision to increased experience and earlier  
275 surgery [63]. As the threshold for revision has not yet been determined, all authorities  
276 recommend revision in patients with imaging abnormalities, especially if progressing, and  
277 rising blood metal ions. This appears reasonable until prognostic factors of outcome are  
278 identified, which are needed to formulate thresholds for revision.

## **Financial analysis of guidelines**

Using MoM hip follow-up guidance from worldwide authorities (Table 1) a financial analysis was performed for common clinical scenarios (Table 2). HR patients with high-risk devices and/or ARMD risk factors were not considered separately because follow-up regimens, and therefore costs, generally parallel those for large-diameter THRs (Table 2: Scenario 1). Follow-up costs have been described previously [65]. The total cost for each scenario represents the annual follow-up of one patient.

Follow-up costs for symptomatic THR and HR patients were the same for each individual authority. However there were large variations in cost per patient between authorities, with USA follow-up costs (£988/€1245/\$1640) three-times that of the MHRA (£330/€416/\$548). For asymptomatic THR patients cost variations were even greater, with those in Australia (£494/€622/\$820) nearly six-times more expensive than the USA and Canada (£84/€106/\$139). In asymptomatic low-risk HR patients costs ranged from those for local protocols (MHRA and Australia) up to £278 (€350/\$461) for European guidance.

By 2012, 67,363 MoM hips (35,470 HR and 31,893 THR) were implanted in the UK [9]. If all these patients were followed up using the most common worldwide protocol (Table 2: annual clinical review, radiographs, metal ions, and MRI) this would equate to £33,277,322/year (€41,899,786/\$55,237,660). However, this estimate is not realistic given follow-up varies between authorities, is based on symptoms, and/or device type.

To more accurately estimate the financial impact of follow-up, data was used from a study of 597 unilateral ASR hips in which 40% of THRs and 16% of HRs were considered to have failed up to seven-years since surgery [36]. Applying these proportions for failed ASR hips to



the original follow-up costs (Table 2) provides a more accurate assessment of the financial implications of surveillance for all MoM hips implanted in the UK when using different protocols (Table 3).

Massive cost differences exist between authorities when considering surveillance of a large population. MHRA guidance was cheapest for annual follow-up (£8,264,064/€10,423,296/\$13,717,440). EFORT (£22,708,226/€28,590,554/\$37,671,431) and the FDA (£22,321,020/€28,134,526/\$37,029,889) were the most expensive protocols, both approaching three-times the MHRA costs. The FDA protocol was the most costly for surveillance of all symptomatic patients (£18,210,816/€22,947,840/\$30,228,480), Australian guidance was most expensive for asymptomatic THRAs (£9,453,184/€11,902,592/\$15,691,520), and EFORTs was most costly for asymptomatic HRs (£8,283,010/€10,428,250/\$13,735,495). The EFORT follow-up protocol was most expensive overall given a large proportion of HRs (84%) were classed as asymptomatic using recent data [36].

## Discussion

Serious concerns were raised regarding patient safety when high failure rates of some MoM hips were publicised [3,8,66,67]. Medico-legal pressures have compounded the problem leading to worldwide authorities issuing guidance based on available evidence. Generally follow-up guidance was conservative to reflect these concerns, but also because ARMD was not well understood. Although our understanding of ARMD has since improved, it remains incomplete. This article provides a novel insight into the contrasting approaches adopted by authorities to follow-up MoM hip patients.

Significant differences exist between protocols, which no longer reflect current evidence. These include not stratifying patients according to implant type (THR or HR) or ARMD risk factors, using symptoms to decide patient follow-up, and using suboptimal blood metal ion thresholds for identifying poorly performing hips. Furthermore, variable information is provided by authorities regarding the collection, processing, and analysis of blood metal ion samples. Each authority must address these issues when updating their guidance, which will help ensure follow-up is more unified between authorities.

The inadequacy of current guidance is highlighted when considering HR patients with asymptomatic ARMD. Four authorities would not identify such patients whilst asymptomatic, as blood metal ions or imaging would not be indicated [16,18-20]. European guidance would identify patients only if blood cobalt was over 2µg/l. A similar situation occurs with THR patients with asymptomatic ARMD. Although ARMD would be identified by cross-sectional imaging in Australia, FDA and Canadian algorithms would not identify such individuals. European guidance would require blood metal ions over 2µg/l for identification, whilst the MHRA requires rising blood metal ions to perform further imaging. In light of this,

consideration should be given to performing baseline cross-sectional imaging in most MoM hips. This would risk stratify patients and therefore inform decisions on subsequent follow-up. However more information is required about the development and progression of ARMD with time before follow-up regularity can be decided. Based on current evidence, modified guidance for MoM hip follow-up has been proposed in Table 4. This can be used in the interim until more robust evidence is available.

Financial implications of current protocols are vast with some countries spending almost three times more on annual follow-up than others. Costs from our analysis are probably conservative given they do not consider the full logistical and resource implications to institutions (extra staff and clinics required, and time taken to perform and report investigations). Despite the almost global cessation of MoM arthroplasty, current follow-up protocols are clearly not financially sustainable in the long-term. What we do know is that certain patients (proven HR designs with no ARMD risk factors) do not require intense follow-up recommended by some authorities. European guidance especially advocates costly follow-up for this subgroup.

Our financial analysis did not consider patients undergoing revision surgery who would be removed from surveillance, as this would have been difficult to integrate into the model. To minimise this, costs for only one-year of follow-up were assessed. Furthermore, geographical variations in cost exist for each aspect of follow-up. Although our estimates may change slightly, by comparing guidance using fixed costs we consider the relationships highlighted between protocols are accurate. Finally, it would have been preferable to extend our analysis to include implant types other than the ASR. Unfortunately this data is not available for large cohorts with all MoM hip designs, with registry data not stratifying patients according to

symptoms [9]. The data used for this analysis included patients comprehensively investigated with current protocols [36], though we recognise this represents a worst case scenario given the ASR is the poorest performing MoM implant.

Questions future research must address include: refining blood metal ion thresholds for concern (especially in bilateral patients) and whether thresholds differ between implants; investigating the reproducibility of metal ion samples (blood and serum) between laboratories; whether MRI or ultrasound should be first-line for imaging; the regularity and duration of follow-up for different patient subgroups; and the threshold for revision surgery. Longitudinal follow-up of large cohorts of MoM hips will answer most questions. This will allow the formulation of optimal evidence-based and cost-effective follow-up guidelines. It is hoped this will reduce current anxieties and concerns in patients not needing regular review and concentrate resources towards those requiring surveillance. It is also expected the development of more evidence-based follow-up will protect surgeons and institutions from a medico-legal perspective.

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**Table 1** Follow-up guidance for large-diameter metal-on-metal hip replacement patients published by worldwide authorities

	<b>MHRA UK [16]</b>	<b>EFORT Europe [17]</b>	<b>FDA USA [18]</b>	<b>TGA Australia [19]</b>	<b>Health Canada [20]</b>
Distinguishes between HR and large-diameter THR	Yes	Yes	No	Yes	No
Follow-up protocol	All THR $\geq 36\text{mm}$ + symptomatic HR – annually for implant life  Asymptomatic HR* - as per local protocol	All THR $\geq 36\text{mm}$ and HR with risk factors**** – annually for implant life  All HR without risk factors - annually for first 5 years (then as per local protocol)	All MoM hips***  Asymptomatic = every 1 to 2 years  Symptomatic = at least every 6 months	All MoM hips with symptoms, & asymptomatic THR $\geq 36\text{mm}$ or HR $\leq 45\text{mm}$ – at least annually  Other MoM hips with no symptoms – as per practice for non-MoM hips	All MoM hips with symptoms – no guidance given on regularity of follow-up  All MoM hips without symptoms - annually for first 5 years (then as per local protocol)***
Follow-up for symptomatic patients	All MoM hips = ions + imaging	All MoM hips = x-ray + ions + imaging	All MoM hips = x-ray + ions + imaging	All MoM hips = x-ray + ions + imaging	All MoM hips = x-ray + ions + imaging
Follow-up for asymptomatic patients	THR = ions**  HR = see above	All MoM hips = x-ray + ions  Further imaging if x-ray abnormal or Co between $2\text{-}7\mu\text{g/l}$	Clinical review	Asymptomatic THR $\geq 36\text{mm}$ or HR $\leq 45\text{mm}$ = x-ray + ions + imaging  Other MoM hips with no symptoms (see above)	Clinical review
Metal ion sampling	Whole blood (Co and/or Cr)	Whole blood (Co only)	Whole blood (Co and/or Cr)	Whole blood or serum (Co and Cr)	Whole blood or serum (Co and Cr)

Metal ion thresholds of concern	>7 µg/l	2-7 µg/l	None stated	None stated	>7 µg/l
Plain radiographs recommended for any patients	Not stated	All patients	Symptomatic patients only	All patients	Symptomatic patients only
Cross-sectional imaging recommended	MARS MRI or ultrasound	MARS MRI or ultrasound or CT	MARS MRI or ultrasound or CT	MARS MRI or ultrasound	MARS MRI or ultrasound
Consider need for revision surgery	If imaging abnormal and/or blood metal ion levels rising	(1) If imaging abnormal and/or blood metal ion levels raised or rising  (2) If Co >20µg/l	Decide in response to overall clinical scenario and test results, but consider early revision in patients with progressive lesions	If persistent symptoms, imaging abnormalities and/or where blood metal ions are rising	If symptoms and positive MRI (soft-tissue mass)  If positive MRI (soft-tissue mass), increasing in size

Cr = chromium; Co = cobalt; CT = computed tomography; EFORT = European Federation of National Associations of Orthopaedics and Traumatology; FDA = Food and Drug Administration; HR = hip resurfacing; MHRA = Medical and Healthcare products Regulatory Agency; MARS MRI = metal artefact reduction sequence magnetic resonance imaging; MoM = metal-on-metal; TGA = Therapeutic Goods Administration; THR = total hip replacement; UK = United Kingdom; USA = United States of America

\* Excludes Articular Surface Replacement hip resurfacing

\*\* Imaging recommended if blood metal ion levels rising

\*\*\* Advises closer follow-up for patients at increased risk of device wear such as females, those with bilateral implants, suboptimal component alignment, or hip resurfacings with small femoral head sizes (less than or equal to 44mm)

\*\*\*\* Risk factors include small femoral head size (<50mm), female gender, and low coverage arc

**Table 2** Financial analysis of follow-up for large-diameter metal-on-metal hip replacement patients in relation to different clinical scenarios

	<b>MHRA UK [16]</b>	<b>EFORT Europe [17]</b>	<b>FDA USA [18]</b>	<b>TGA Australia [19]</b>	<b>Health Canada [20]</b>
<b>Scenario 1</b> Large-diameter MoM THR ( $\geq 36$ mm) Symptomatic	Clinical review, metal ions, MRI	Clinical review, x-ray, metal ions, MRI	Clinical review, x-ray, metal ions, MRI x 2*	Clinical review, x-ray, metal ions, MRI	Clinical review, x-ray, metal ions, MRI
Cost of 1 year follow-up for 1 patient	£330 €416 \$548	£494 €622 \$820	£988 €1245 \$1640	£494 €622 \$820	£494 €622 \$820
<b>Scenario 2</b> Large-diameter MoM THR ( $\geq 36$ mm) Asymptomatic	Clinical review, metal ions	Clinical review, x-ray, metal ions	Clinical review	Clinical review, x-ray, metal ions, MRI	Clinical review
Cost of 1 year follow-up for 1 patient	£114 €144 \$189	£278 €350 \$461	£84 €106 \$139	£494 €622 \$820	£84 €106 \$139
<b>Scenario 3</b> HR Low-risk patient Symptomatic	Clinical review, metal ions, MRI	Clinical review, x-ray, metal ions, MRI	Clinical review, x-ray, metal ions, MRI x 2*	Clinical review, x-ray, metal ions, MRI	Clinical review, x-ray, metal ions, MRI
Cost of 1 year follow-up for 1 patient	£330 €416 \$548	£494 €622 \$820	£988 €1245 \$1640	£494 €622 \$820	£494 €622 \$820
<b>Scenario 4</b> HR Low-risk patient Asymptomatic	Local protocol	Clinical review, x-ray, metal ions	Clinical review	Local protocol	Clinical review
Cost of 1 year follow-up for 1 patient	£0 €0 \$0	£278 €350 \$461	£84 €106 \$139	£0 €0 \$0	£84 €106 \$139

EFORT = European Federation of National Associations of Orthopaedics and Traumatology; FDA = Food and Drug Administration; HR = hip resurfacing; MRI = magnetic resonance imaging; MHRA = Medical and Healthcare products Regulatory Agency; MoM = metal-on-metal; TGA = Therapeutic Goods Administration; THR = total hip replacement; UK = United Kingdom; USA = United States of America



All scenarios assume patients have unilateral metal-on-metal hip implants, the device has not been recalled, and the implant has an acceptable radiographic position.

The costs for each aspect have been taken from a previous publication [65]:

outpatient follow-up appointment = £84 (€106/\$139), radiographs (anteroposterior pelvis and lateral hip) = £164 (€207/\$272), magnetic resonance imaging = £216 (€272/\$359), blood sampling for cobalt and chromium ion concentrations = £30 (€38/\$50).

An ultrasound scan is the cheapest cross-sectional imaging modality (£49/€62/\$81) therefore for the purposes of this analysis the modality used for calculating costs was magnetic resonance imaging as this was the most expensive.

Conversion rates for total costs: £1 = €1.26; £1 = \$1.66

\* 6-monthly follow-up recommended for symptomatic patients in the USA therefore costs doubled to provide costing for 1 year.

The cost of local protocol follow-up has been taken to be zero for the purposes of this analysis (at this institution all asymptomatic patients with low risk hip resurfacing devices with no adverse reaction to metal debris risk factors were discharged).

**Table 3** Differences in cost for annual follow-up for all metal-on-metal hip replacements in the United Kingdom (n=67,363) when using various worldwide protocols

	<b>MHRA UK [16]</b>	<b>EFORT Europe [17]</b>	<b>FDA USA [18]</b>	<b>TGA Australia [19]</b>	<b>Health Canada [20]</b>
Large-diameter MoM THR (≥36mm) Symptomatic  <b>n = 12,757</b>	£4,209,810 €5,306,912 \$6,990,836	£6,301,958 €7,934,854 \$10,460,740	£12,603,916 €15,882,465 \$20,921,480	£6,301,958 €7,934,854 \$10,460,740	£6,301,958 €7,934,854 \$10,460,740
Large-diameter MoM THR (≥36mm) Asymptomatic  <b>n = 19,136</b>	£2,181,504 €2,755,584 \$3,616,704	£5,319,808 €6,697,600 \$8,821,696	£1,607,424 €2,028,416 \$2,659,904	£9,453,184 €11,902,592 \$15,691,520	£1,607,424 €2,028,416 \$2,659,904
HR Symptomatic  <b>n = 5,675</b>	£1,872,750 €2,360,800 \$3,109,900	£2,803,450 €3,529,850 \$4,653,500	£5,606,900 €7,065,375 \$9,307,000	£2,803,450 €3,529,850 \$4,653,500	£2,803,450 €3,529,850 \$4,653,500
HR Asymptomatic  <b>n = 29,795</b>	£0 €0 \$0	£8,283,010 €10,428,250 \$13,735,495	£2,502,780 €3,158,270 \$4,141,505	£0 €0 \$0	£2,502,780 €3,158,270 \$4,141,505
<b>Total annual cost for follow-up of all MoM hips using each particular protocol</b>	£8,264,064 €10,423,296 \$13,717,440	£22,708,226 €28,590,554 \$37,671,431	£22,321,020 €28,134,526 \$37,029,889	£18,558,592 €23,367,296 \$30,805,760	£13,215,612 €16,651,390 \$21,915,649

EFORT = European Federation of National Associations of Orthopaedics and Traumatology; FDA = Food and Drug Administration; HR = hip resurfacing; MHRA = Medical and Healthcare products Regulatory Agency; MoM = metal-on-metal; TGA = Therapeutic Goods Administration; THR = total hip replacement; UK = United Kingdom; USA = United States of America

**Table 4** Proposed follow-up guidance for large-diameter ( $\geq 36$ mm) metal-on-metal hip replacement patients based on current evidence

	<p><b><u>THR</u></b></p> <p>- All patients (regardless of symptoms)</p> <p><b><u>HR</u></b></p> <p>- All patients (regardless of symptoms) who have recalled or withdrawn implants or designs with a poor track record</p>	<p><b><u>HR</u></b></p> <p>- All symptomatic patients and asymptomatic patients with ARMD risk factors* with established implant designs</p>	<p><b><u>HR</u></b></p> <p>- All asymptomatic patients without ARMD risk factors* with established implant designs</p>
Follow-up required	<ul style="list-style-type: none"> <li>- Clinical review</li> <li>- Radiographs (AP pelvis + lateral hip)</li> <li>- Metal ions (whole blood or serum)</li> <li>- Cross-sectional imaging (MARS MRI or ultrasound)</li> </ul>	<ul style="list-style-type: none"> <li>- Clinical review</li> <li>- Radiographs (AP pelvis + lateral hip)</li> <li>- Metal ions (whole blood or serum)</li> <li>- Cross-sectional imaging (MARS MRI or ultrasound)</li> </ul>	<ul style="list-style-type: none"> <li>- Clinical review</li> <li>- Radiographs (AP pelvis + lateral hip)</li> <li>- Metal ions (whole blood or serum)</li> </ul>
If normal (including metal ions $< 2 \mu\text{g/l}$ )	Review in 2 years	Review according to local protocol**	Review according to local protocol**
If abnormal (including metal ions $\geq 2 \mu\text{g/l}$ )	Review in 1 year OR Consider revision	Review in 1-2 years OR Consider revision	Cross-sectional imaging (MARS MRI or ultrasound)
Threshold for revision surgery	If imaging abnormal and/or progressing and/or blood metal ion levels rising and/or hip symptomatic with no other cause identified	If imaging abnormal and/or progressing and/or blood metal ion levels rising and/or hip symptomatic with no other cause identified	If imaging abnormal and/or progressing and/or blood metal ion levels rising

AP = antero-posterior; ARMD = adverse reactions to metal debris; HR = hip resurfacing; MARS MRI = metal artefact reduction sequence magnetic resonance imaging; THR = total hip replacement

\* ARMD risk factors include: female patients, hip diagnosis other than primary osteoarthritis, suboptimal component alignment [28], small femoral head sizes ( $< 46$  mm), and those with bilateral metal-on-metal hip implants.

\*\* These patient subgroups may require a repeat assessment after a certain time interval depending on the results of future longitudinal cohort studies.

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