Results of the public consultation on SCENIHR's preliminary opinion on Safety of Metal-on-Metal joint replacements with a particular focus on hip implants

A public consultation on this opinion was opened on the website of the Scientific Committees from 13 March to 25 April 2014. Information about the public consultation was broadly communicated to national authorities, international organisations and other stakeholders.

14 organisations and individuals participated in the public consultation providing 51 comments to different chapters and section of the opinion. Each submission was carefully considered by the Working Group and the scientific opinion has been revised to take account of relevant comments. The literature has been accordingly updated with relevant publications. The scientific rationale and the opinion section were clarified and strengthened.

The table below shows all the comments made about each of the questions posed in the opinion and SCENIHR's response to them. It is also indicated if the comment resulted in a change of the opinion.

Comments received during the public on the SCENIHR preliminary opinion on "Safety of Metal-on-Metal joint replacements with a particular focus on hip implants"

SUBMISSIONS			SCENIHR'S COMMENTS
Name of individual/ organisation	**Table of content to which comment refers**	**Comment**	**SCENIHRs Response**
TRACOL Philippe; Sofcot; phtracol@orange.fr; France	1. EXECUTIVE SUMMARY	This document is a full meta-analysis on the subject. This completes the European and French consensus. The SOFCOT take note and has no specific comments to make.	SCENIHR thanks SOFCOT for the comment.
Joyce Thomas; Newcastle University; thomas.joyce@ncl.ac.uk; United Kingdom	1. EXECUTIVE SUMMARY	On page 9 it is stated that 'The most common cause of failure was fracture of the femoral neck'. However, data from the Australian Joint Registry contradicts this view. The 2010 Australian Orthopaedic Association arthroplasty register records the overall risk of fracture at 9 years as 2.6%, though the incidence occurs mainly in the first year after surgery and only very slightly thereafter. The same source records cumulative revision rates for resurfacing devices in the same time frame as 7.2%. As such, fractures represent a significant (35.6%) but not majority percentage of overall resurfacing failures.	SCENIHR thanks Joyce Thomas for the comment. The sentence 'The most common cause of failure was fracture of the femoral neck' refers to the described results of a multicentre study from 11 centres (Canadian Arthroplasty Society 2013), which is described in detail also on page 21. Although the statement holds true for the cited study with 2773 resurfacing patients with a 5-year observation period, it can of course not be generalized. In order to avoid misunderstanding, the sentence was deleted in a revised Executive Summary.
Joyce Thomas; Newcastle University; thomas.joyce@ncl.ac.uk; United Kingdom	1. EXECUTIVE SUMMARY	On page 8 it is stated 'the higher observed MoM-revision rate is mainly caused by the poor survival rates of large-head THA and HRA, if they are not implanted properly'. I feel this is not quite the full story. If the DePuy ASR is considered the 2012 Australian joint registry shows very little difference in revision rates between 'low' volume and 'high'	SCENIHR thanks Joyce Thomas for the comment. Improper acetabular cup placement (i.e. high inclination and anteversion) as well as other technical errors (i.e. notching of the femoral neck) are recognized risk factors for worse outcome in HRA. Nevertheless the sentence 'the higher observed MoM-

		volume surgeons. Specifically, 5 year revision rates are as follows, for surgeons performing >10 to ≤25 procedures per year 22.8%, for surgeons performing >25 and ≤70 and 23.3%, and for surgeons performing >70 procedures per year 21.8%. In addition, the Langton et al paper (J Bone Joint Surg Br 2011; 93(2):164-171 – already referenced in your document) showed 3 high volume surgeons obtained similar acetabular cup positions but very different revision rates between 3 types of hip resurfacing – ASR, BHR and Conserve Plus. Therefore design differences (arc of cover) are more important in hip resurfacing, than cup positioning. It is also our view that, in the case of the DePuy ASR XL and the DePuy MoM Pinnacle, cup position has relatively little influence on revision rates. On page 9 it is stated that 'the most common cause of failure was fracture of the femoral neck'. However there is some contradictory data. The 2010 Australian Orthopaedic Association arthroplasty register records the overall risk of fracture at 9 years as 2.6%, though the incidence occurs mainly in the first year after surgery and only very slightly thereafter. The same source records cumulative revision rates for resurfacing devices in the same time frame as 7.2%. As such, fractures represent a significant percentage (35.6%) of overall resurfacing failures but not the majority. On page 11 (and later page 26) it is stated that 'It must be emphasised that wear rate and metal ion release of the historic McKee-Farrar prosthesis are substantially higher than those of modern design MoM implants'. I am not sure where this view has been taken from. The opposite could be the case. Tuke et al, 2008, JBJS, 90, Supp III, 134-41, offered wear volumes from 5 explanted first generation metal-on-metal hips (their table 1). Wear rates were 1.1-7mm3/year. These compare with wear rates of 0.5 to 95.5mm3/year (over 10 times	revision rate is mainly caused by the poor survival rates of large-head THA and HRA, if they are not implanted properly' does indeed exclude other important risk factors like for example design (especially from discontinued devices) and size of implants. Therefore SCENIHR changed The Executive summary. A comment on "femoral neck fractures' has been given above. Retrievals showed that wear in some of the original McKee Farrar prostheses was very small, e.g.: Clarke MT, Darrah C, Stewart T, Ingham E, Fisher J, Nolan JF. J Arthroplasty. 2005 20(4):542-6. Long-term clinical, radiological and histopathological follow-up of a well-fixed Mckee-Farrar metal-on-metal total hip arthroplasty. Łapaj Ł, Markuszewski J, Wierusz-Kozłowska M, Rybak T. Pol Orthop Traumatol. 2012 Jun 4;77:17-20. 30-year survival of a McKee-Farrar hip prosthesis--case report and microscopic analysis of bearing surface. Howie DW, McCalden RW, Nawana NS, Costi K, Pearcy MJ, Subramanian C.J Arthroplasty. 2005 Apr;20(3):350-7. The long-term wear of retrieved McKee-Farrar metal-on-metal total hip prostheses. On the other side, overall the McKee-Farrar prostheses failed but probably rather due to high friction caused by manufacturing tolerances (loosening): Zahiri CA, Schmalzried TP, Ebramzadeh E, Szuszczewicz ES, Salib D, Kim C, Amstutz HC J Arthroplasty. 1999 Apr;14(3):326-32. Lessons learned from loosening of the McKee-Farrar metal-on-metal total

		greater) which we have reported for ASR hip resurfacings (Lord et al, Wear, 2011, 272, 1, 79-87). It should also be appreciated that HR and LHMoM tend to have larger articulating radii than first generation MoM hips. If the HR and LHMoM articulating surfaces roughen and move into boundary lubrication (as shown by Joyce et al, 2009, J Engineering Tribology) then the wear volume per cycle will increase in proportion to the radius. Moreover, first generation MoM hips tended to be monoblock and so lack any concerns over metal release from taper junctions between femoral heads and femoral stems.	hip replacement. Täger G, Euler E, Plitz W Orthopade. 1997 26(2):142-51. [Changes in shape of the McKee-Farrar hip endoprosthesis]. [Article in German] McKellop H, Park SH, Chiesa R, Doorn P, Lu B, Normand P, Grigoris P, Amstutz H Clin Orthop Relat Res. 1996 Aug;(329 Suppl):S128-40. In vivo wear of three types of metal on metal hip prostheses during two decades of use.. The comment regarding monobloc designs is a good one, but probably overruled by the large deviations in dimensions. Please see the new Executive summary Suggested Change p. 22: "Although this conclusion is limited by a relatively small cohort size, it is important to note that wear rate and metal ion release in some of the historic McKee-Farrar prosthesis was substantially higher than those of modern design MoM implants due to the higher dimensional tolerances. Similar amounts of metallic debris can be expected with modern implants in unfavorable wear situations in the patient resulting in boundary lubrication."
Kjaersgaard-Andersen Per; EFORT (European Federation of National Associations of Orthopaedics and Traumatology; pka@dadlnet.dk; Denmark	1. EXECUTIVE SUMMARY	• Orthopaedic surgeons must by guided on how to follow-up in details on patients with a MoM implant. Therefore, recommendations on how frequent to follow-up, and with what tools must have a high priority in the final document, with its own paragraph in the Executive Summary. The question will be if this is a regularly (i.e. annual) lifelong follow-up for all MoM implants? • Also, a detailed summary is needed in the Executive Summary	SCENIHR thanks EFFORT for the comment. It is indeed important to provide recommendations for patient follow-up including indications for revision. Chapter 4.6 summarises recent opinions. However, the currently available recommendations from several health authorities, scientific societies and single centre opinions are not in agreement. In order to provide at least a widely recognized current statement, we have

		regarding indication for revision of a MoM hip implant. This is a frequent asked and debated question among surgeons and from patients. • Data from National Joint Replacement Registeries are extremely important in monitoring and for future conclusions on MoM implants. Therefore the document should include detailed recommendations to the registries on their frequency and type of reports on MoM implants. • The document mainly focuses on MoM hip implants as a group – or three groups (resurfacing, large-head and small head). As one MoM brand (product) may have very different outcomes from other MoM brands, recommendations, conclusions and reports must be related to the single brand. • The document should stress National Societies and Supranational Organisations, based on this document, to create – and regularly update guidelines to follow-up of and information to patients with a MoM hip implant, and treatment including indication for revision of the MoM hip. • Metal ions blood levels and pathologies in the soft tissue around the replaced hip using ultrasound, CT or MRI-scanning of non MoM hip arthroplasty implants must have a major priority in future research on total hip replacement outcomes, to stress the factual level of problems with all types of total hip implants.	cited the European multidisciplinary consensus (2013) in detail (see chapter 4.6.2.). SCENIHR considers that , however, the evidence of this as well as other opinions are currently not strong enough to integrate it into the executive summary.. The comments on registries, guidelines and investigation of other artificial implants are included in research recommendations (chapter 4.8.).
Trusler Julia; British Hip Society/British Orthopaedic Association; j.trusler@boa.ac.uk; United	1. EXECUTIVE SUMMARY	The attached statement has been prepared by the British Hip Society and endorsed by the British Orthopaedic Association and represents a unified statement on behalf of British Orthopaedics on this document.	SCENIHR thanks British Hip Society/British Orthopaedic Association for their contribution.

Kingdom			
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	1. EXECUTIVE SUMMARY	Executive summary, 8 "In the early 1960s, Metal-on-Metal (MoM) hip implants began to replace "conventional" systems consisting of metal-on-polyethylene (MoP) or ceramic-on-ceramic (CoC) joints". Eucomed believes the above statement to be incorrect and, in fact, is then contradicted by the following statements. Metal-on-metal total hip arthroplasty has the longest clinical history of any of the currently used articular couples and was already used widely (McKee Farrar, Ring, Sivash) before the introduction of Charnley's 'low friction arthroplasty (LFA)' that popularised the use of metal-on-polyethylene. Ceramic-on-ceramic was introduced in the early 1970s. Pierre Boutin in collaboration with Ceraver Inc. first reported on the clinical results of CoC hip arthroplasty in 1971. By the mid-1980s there were significant improvements in machining and finishing of metal bearings and therefore, the reintroduction of MoM was not at all unreasonable as it is suggested in the report. Therefore, it is not correct to suggest that MoM was in any way 'unconventional' or new and not reasonable at the time.	SCENIHR thanks Eucomed for the comment. The Executive Summary was changed.
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	1. EXECUTIVE SUMMARY	Executive summary – "Product survival rate of MoM implants", 8 "However, the higher observed MoM-revision rate is mainly caused by the poor survival rates of large-head THA and HRA, if they are not implanted properly". - All devices must be evaluated individually as there exist differences in design, materials and clinical performance. - As acknowledged in the statement itself ("Not implanted properly"), the surgical technique plays a major role in the performance and	SCENIHR thanks Eucomed for the comment. The Executive summary was changed taking into account this comment.

		survival rate of THA and HRA. This is not device related. "For small-head THA with a head diameter of <36mm, the 11-year survival rate of MoM implants from registries is comparable to the survival of other hard-on-hard bearings". Eucomed considers that both surgeon (i.e. qualification and experience) and patient related factors have to be taken into consideration. For example patient with SHMOM may have different baseline and required post-op activity level compared to LHMOM cases.	
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	1. EXECUTIVE SUMMARY	Executive summary – "Product survival rate of MoM implants", 9 "In spite of the obligation of manufacturers for post-market follow-up, there are no long-term studies available for large-head MoM THA" - This statement reads as if manufacturers do not comply with applicable regulations. Eucomed believes that its members as a matter of principle do comply with all applicable rules and regulations, as it is also a condition for Eucomed's membership. More specifically, orthopaedic member companies have reported that they closely monitor the clinical performance of their implants including MoM hip implants via review of post market surveillance data consisting of data from the national joint registers, post market surveillance studies, published results in literature and complaint data. - SCENIHR is invited to provide their definition of "long term". "Moreover, some registries confirmed the bad performance of these implants with reports of 10-year cumulative percent revision of MoM-THA with a head diameter of 36mm and more being four times higher (20.3%) than the cumulative percent revision of CoC bearings with a similar diameter. The failures may be caused by a combination of elevated metal ion release and fretting corrosion at the taper due to the large head diameter. Some MoM large-head implants were recalled from the market due to their bad performance" - Devices must be evaluated individually as differences in design,	SCENIHR thanks Eucomed for the comment. The Executive summary was changed taking into account this comment. In this opinion, "long term" is used for studies covering 10 or more years of follow up. This is on pages 4, 8 and 21. The terms "bad performance" and "Higher than expected revision rates" are not the clearest terms but are commonly used in this field to indicate failure and short survival rates.

		materials and clinical performance exist, and therefore this generalisation is inappropriate. - Moreover, as mentioned above, reported revisions may be caused as well by device mal-positioning as by other non-device related reasons for revision of the MoM THA. - It is unclear what "bad performance" means. Eucomed would advise the SCENIHR to focus on specific measures such as higher than expected revision rates etc.	
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	1. EXECUTIVE SUMMARY	Executive summary – "Product survival rate of MoM implants", 9 "The most common cause of failure was fracture of the femoral neck" Reports of fracture of the femoral neck can be related to the procedure and not to the device. We would therefore advise to use the term "revision" and not "failure".	SCENIHR thanks Eucomed for the comment. The sentence has been deleted (see above).
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	1. EXECUTIVE SUMMARY	Executive summary – "Product survival rate of MoM implants", 10 "Theoretically, metal implants may have associated adverse effects in all tissues and organs of the body. However, published evidence on metal-related systemic toxicity in patients with hip arthroplasty and specifically with MoM implants is limited. In some case studies, the potential clinical picture of "arthroprosthetic cobaltism" is highlighted." - Eucomed agrees with the statement that clinical evidence is scarce. A recent paper on systemic effects attributed to a MoM device was presented by J. M. Wilkinson, MD, Sheffield, United Kingdom at the 2014 AAOS (New Orleans) during the symposium "Metal on Metal and Modular Corrosion: Clinical Impact of Tribocorrosion", 12 March. Based on this literature review, Prof. Wilkinson found it difficult to determine if there were truly any systemic effects that can be attributed to a MoM device. We understand that 'arthroprosthetic cobaltism' is not a widely recognised medical condition and has only been used by a	SCENIHR thanks Eucomed for the comment. The recent paper by Wilkinson et al. is certainly of value, but does not add new insights, because it is not a peer reviewed paper. Therefore, the weight of evidence is low and was therefore not used in the opinion.

		limited number of authors.	
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	1. EXECUTIVE SUMMARY	Executive summary – "Conclusions of factors influencing the health outcome: surgeon, patient and the implant per se", 13 "While resurfacing may be an option in a highly selected subgroup of patients (i.e. especially young and active male patients with bony femoral head size > = 50mm and favorable head-neck-ratio), the implantation of large-head MoM THA should be avoided in other patient groups. - SCENIHR is invited to define what they consider to be a "favorable head-neck ratio".	SCENIHR thanks Eucomed for the comment. Among other factors, the relationship between femoral head size and femoral neck diameter (head-neck-ratio) is an important predictor of the range of motion in native hips as well as in artificial hips. Distinct values for favourable head-neck-ratios have been calculated for conventional THA (Patel and Goswami. Med Eng Phys 2012; 34:573-8). Femoral neck preservation in HRA generally decreases the head-neck ratio over conventional THA and leads to a higher risk of impingement. Grammatopoulos et al (Hip Int. 2012; 22(3):266-73) have shown that among other factors the head-neck-ratio effects hip flexion significantly in HRA. They as well as other authors did, however, not provide defined thresholds for "favourable" head-neck-ratios. It is generally agreed that large head neck ratios result in a greater arc of impingement free motion. For clarification, the term "large" was added to the sentence about 'favourable head-neck ratios' in the opinion on page 9 and page 42.
Labek Gerold; European Arthroplasty Register; gerold.labek@efort.org; Austria	1. EXECUTIVE SUMMARY	Ladies and Gentlemen, This is a statement on the preliminary opinion with a particular focus on methodology and arthroplasty register data. • Randomised clinical studies are of limited value for the questions under consideration since the numbers included are usually low and the statistical power is minimal. Leading regulators are currently changing the processes for market monitoring (cf. MDD at EU level). This aspect has not been given adequate consideration in the present document. To achieve sufficient statistical power, relatively rare events	SCENIHR thanks European Arthroplasty Register for the comment. Randomised clinical studies are a powerful tool, and these types of studies generate useful data to review patient outcome. Although low numbers reduce the power and certainty, the significance in low power studies is meaningful. In the current opinion, the current situation is described without predictions on which changes will be finally implemented. We did not add confidence intervals for the readability of the document. In the main conclusion, in some occasions, technologies were

		like revision surgery, local or systemic effects (cancerogenicity, etc.) can only be reasonably analysed through large datasets; sample-based clinical studies are of limited use in this setting. When referring to outcome data, at least confidence intervals should be provided to address differences in numbers regarding the individual cohorts. • Different technologies were mixed; Low Carbide MoM implants, for example, were in fact associated with unsatisfactory results, but they have meanwhile been withdrawn from the market. This fact is not mentioned and does not seem to have been sufficiently considered in the conclusions. (Page 8, Small Head MoM THA) Large diameter head implants, resurfacing and low diameter head implants should be assessed as separate groups. • Many implanted medical devices are made of metal. In some passages of the text a clearer distinction between simple metal products and wear between articulations (as intended by the design or not like in a taper junction) might be useful. Some statements (like correlation between metal surface of knee implants and relevant metal ion levels in blood samples) are not supported by evidence and remain inconclusive from an orthopaedic expert point of view. • The mention that there are significant differences between individual implants per group is correct; but the conclusions and recommendation provide only limited reference to this issue. • A significant part of the document deals with potential systemic effects of MoM, extensive efforts have been made to review the relevant literature. Nevertheless there is little evidence for the effects mentioned while potential side effects are explained in quite some detail several times. Conclusions do not seem to be based on entirely solid evidence in this context. Various effects are mentioned, some conclusions remain speculative in terms of their relevance for the topic under evaluation;	grouped to reduce the complexity. Nevertheless, care was taken not to generalise. Many different types of implants are made of metal. The correlations given in the opinion are based on peer reviewed publications. Some attention is paid to systemic effects, and only data referring directly to implants were included, e.g. no general toxicity data of different metals was included in the opinion. Using the current database, it is not possible to verify all conclusions (in either direction), therefore some precaution is needed. In the background section, it is explained on which rationales the 'terms of reference' were based (before emerging the opinion). In the opinion, text found beyond the Terms of Reference, more data was included.

		some statements are based on small cohorts that might be subject to various confounders (metal allergy, systemic toxicity, etc.). Large cohorts from registries have been published on potential side effects, the risk ratios of systemic effects appeared relatively low on average; it should be considered that specific items were studied, but not published since no statistically significant increase of risk was measured. Pretty exhaustive and expensive actions are proposed to gain evidence on that subject. At least risk estimations on the volume of potential effects should be presented as a rationale for this proposal. • Page 14, Background: The number of MoM hip replacements seems to be underestimated. One reason might be that Great Britain, as the main user in the European Union, was not included in the estimation according to the declaration the footnote. The latest Annual Report by the National Joint Registry, covering mainly England and Wales, indicates that the numbers implanted in GB might be close to 100,000, mentioned as number of patients at risk in the entire European Union. (Ref: NJR 10th Annual Report, p. 79)	
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	2. BACKGROUND	Background,14 “Besides their use in hip arthroplasty, metal alloy implants have been used successfully in orthopaedics for years, for example in knee operations and fracture repair. All metal implants are known for release of metal ions due to corrosive processes, but some MoM prostheses do so in much greater extent than previously thought”. - Eucomed would like to point out that titanium-aluminium-vanadium alloy, cast and wrought cobalt-chromium-molybdenum alloy and hydroxyapatite coating are complying with the applicable ISO standards and identified within BS EN ISO 21534 Annex A as materials found acceptable for the manufacture of implants through proven clinical use.	SCENIHR thanks Eucomed for the comment. No changes in the opinion required.

Joyce Thomas; Newcastle University; thomas.joyce@ncl.ac.uk; United Kingdom	4.1. Introduction	On page 16 it is stated that 'Tribological and clinical studies have described a characteristic wear pattern of MoM hips which is initially characterised by a high-wear running-in period, followed by a lower-wear steady-state'. While this has been reported from several simulator studies I do not think this is always the case in vivo. Our published measurements from explanted MoM hips show high wear after the short durations which might be termed the 'running-in period' (Joyce el al, 2011, Tribology International; Lord et al, 2011, Wear). Moreover this wear result is supported by roughness results which show an increase in roughness [NOT the decrease in roughness expected of running-in] and a move towards boundary lubrication with its concomitant high wear (Joyce et al, 2009, J Eng Tribology). In a simulator study Williams et al showed that a constant, high wear rate from a HR was possible when smaller HRs were tested at 'sub-optimal' cup inclinations (Williams et al, 2008, JBJS). Furthermore the in vitro results of Williams et al correspond closely with the ex vivo results of Lord et al, 2011.	SCENIHR thanks Joyce Thomas for the comment. Clinically, in failed prostheses the "running in" was not observed since they did not 'run in' and went into boundary lubrication right from the beginning or from early on. For the retrievals without rim loading, the expected low wear rate was found after running in . To address this, we referred to the following: Thomas J. Joyce, Harry Grigg, David J. Langton, Antoni V.F. Nargol, Quantification of self-polishing in vivo from explanted metal-on-metal total hip replacements, Tribology International, Volume 44, Issue 5, May 2011, Pages 513-516 Morlock MM, Bishop N, Zustin J, Hahn M, Rüther W, Amling M J Bone Joint Surg Am. 2008 Aug;90 Suppl 3:89-95. doi: 10.2106/JBJS.H.00621. Modes of implant failure after hip resurfacing: morphological and wear analysis of 267 retrieval specimens. SCENIHR has changed the text on p.12, which is now " Bacteriological and clinical studies in hip simulators have described a characteristic wear pattern of MoM hip implants which is initially characterised by a short high-wear running-in period, followed by a lower-wear steady-state. This was clinically only observed for prostheses, which did not show signs of rim loading at revision (Joyce et al., 2011; Morlock et al., 2008)
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.1. Introduction	4.1., Introduction, 16 -The Preliminary Opinion makes reference to registry data that large diameter (≥36mm) MoM THA are associated with a high revision rate,	SCENIHR thanks Eucomed for the comment. We agree, that the division between head sizes <36mm and ≥36mm is arbitrary (see page 16 of the opinion). As pointed out in

		and that MoM implants with ≥36mm diameter heads have a lower survival rate than heads <36mm. One of Eucomed's members indicated that it has data on the ULTAMET MoM(1) system demonstrating that the survivorship reported in the UK NJR is not affected by the head size with equivalence being reported for sizes <36mm and ≥36mm. The survivorship of the ULTAMET MoM system is reported to be in line with or better than other MoM systems evaluated in the 2011 and 2012 AOA NJRR reports. More recent analysis of the March 2014 NJR data for Pinnacle MoM also shows there is no significant difference in survivorship between the <36mm group and the ≥36mm group. This company will request permission from the NJR to provide the Scientific Committee the data to review if requested. Eucomed suggests as per the summary, that this head-size division is arbitrary and not helpful given the known differences in product design and materials.	Chapter 4.2.1, we are using this discrimination because most of the recently published recommendations are also using it. The head size is only one risk factor among many others. Although we have considered this, we added remarks about heterogeneous survival rates even in the large-head group of implants on pages 9, 17 and 20.
Cirstoiu Catalin; Romanian Socity of Orthopaedy and Traumatology , University of Medecine Bucharest; cirstoiu_catalin@yahoo.com; Romania	4.2.1.2. Hip resurfacing (HRA)	I start to use hip resurfacing implants eight years ago. I realise 65 THR with ASR hip system. Two of them had a very fulminant evolution due to a bad indication (osteoporosis). We realise the serum determination for Co and Cr and we start to identify a high serum concentration for 9 implants, but with a good clinical and radiological evolution.	We thank the Romanian Society of Orthopaedics and Traumatology for the comment. No changes of the opinion required.
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.2.2. Metal wear and degradation products	4.2.2., "Metal wear and degradation products", 19 "Several different metal alloys are used in Metal-on-Metal (MoM) implants. The bearing surface itself is mostly made from CoCrMo-alloys. They may in addition contain small amounts of nickel (Ni), iron (Fe), manganese (Mn), silicon (Si) and vanadium (V)." - All current metal on metal implants are manufactured from cast or wrought CoCrMo alloy. In the case of cast CoCrMo, the alloy may be as-	SCENIHR thanks Eucomed for the comment. As mentioned before, in this Opinion it is never questioned whether materials used were or were not in line with ISO standards.

		cast or cast and heat-treated. Ti- and/or hydroxyapatite coatings may also be applied to enhance bone attachment on the acetabular components. Cast and wrought cobalt-chromium-molybdenum alloy and Ti- and /or hydroxyapatite coating are complying with the applicable ISO standards and identified within BS EN ISO 21534 Annex A as materials found acceptable for the manufacture of implants through proven clinical use.	
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.3.1.1. Small-head MoM THA	4.3.1.1., "Small Head MoM THA", 20 - Given that it is generally agreed that device performance is multifactorial and not related to a single design feature, Eucomed notes that while the design of the bearing articulation has been correlated to the survivorship of metal bearings, the issue of specific design features is not addressed. Poor results are being associated with low carbide content of the bearing materials, but no mention is made of the interplay of other design features, e.g., surface roughness, sphericity, diametrical clearance, surface contact, etc. cited as other possible correlating factors affecting device survivorship.	SCENIHR thanks Eucomed for the comment. Although we agree with the comment, that different design features affect the performance of small-head MoM THA, there is not enough evidence from clinical studies, to correlate implant design with clinical survival rates. No changes to the opinion are required in relation to the comment.
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.3.1.2. Large-head MoM THA	4.3.1.2., "Large head MoM THA", 20 - The poor performance of large head MoM devices when compared to MoP or CoC device survivorship is specifically correlated to local and/or systemic toxicity from the metal ions or from metal wear debris from the taper junction. This conclusion is different from the one cited for small head (<36mm diameter) MoM devices and does not address other factors. The opinion also refers to a 'projected 37% revision rate at less than five years and has recalled this product from the market'. This statement is incorrect for two reasons: Firstly, the projected revision rates was for all reasons and not just pseudotumours and secondly, the	SCENIHR thanks Eucomed for the comment. The information in the Opinion is extracted from studies (which are clearly cited). In the comment two different studies are wrongly taken together (the study of Meyer et al 2012 and the recall.) No changes to the opinion are required in relation to the comment.

		decision to recall was based on information from the England and Wales National Joint Register. It is important that the sources of information from which the assessment of the safety and performance of the MoM devices was made is provided, in order to give the context of how the information is presented.	
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.3.1.2. Large-head MoM THA	4.3.1.2., "Large head MoM THA", 20 In the series of Bolland et al (2011) 31 revisions had to be performed in 185 patients with BHR®- and Adept®-implants 5 years postoperatively." - This statement appears in the chapter discussing the clinical outcomes of Large-head MoM THA. It refers to Birmingham Hip Modular Head components as "BHR", which may confuse the reader. BHR only refers to RHA, where it demonstrates class-leading clinical performance, as noted elsewhere in the report. Eucomed would like to request that the reference to BHR be changed to Birmingham Hip Modular Head MoM THA.	SCENIHR thanks Eucomed for the comment. This comment is not correct, as Bolland et al have written in their article: "On the acetabular side, the Birmingham Hip Resurfacing (BHR) acetabular compo- nent (Smith & Nephew, Warwick, United Kingdom) coupled with a large modular metal femoral head (Midland Medical Technologies (MMT) Ltd, Birmingham, United Kingdom) was used until 2006, when they were replaced by the Adept resurfacing actabular component and modular metal heads (Finsbury Orthopaedics, Leatherhead, United Kingdom)..." Nevertheless on page 16 the term BHR in the Opinion was misleading and we have changed it accordingly (see p 16)
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.3.1.3. Hip resurfacing arthroplasty (HRA)	4.3.1.3., "Hip resurfacing arthroplasty (HRA)", 21 "In contrast, Sehatzadeh et al (2012) stated in a more recently performed Ontario Health Technology Assessment with analysis of six different implants that available revision rates for HRA with three implants (BHR®, ConservePlus®, and Cormet®) met the NICE criteria. Two implants had only short-term follow-ups (Re-Cap®, DUROM®) and resurfacing with one of the implants (ASR®) failed to meet the NICE criteria." - Eucomed believes that comparison of ASR to other products or any guidelines has only limited value due to the fact that ASR was recalled. Such recalls, as observed with the 3M Capital hip recall, are known to have a significant effect on revision rates which tend to increase.	SCENIHR thanks Eucomed for the comment. While for other implants and bearing materials numerous systematic investigations and even meta-analyses (Kuzyk et al: Crosslinked versus conventional polyethylene in THR. J Bone Joint Surg-B 2011; 93B:593-600) have been performed in order to investigate wear-related adverse events, the number of investigations concerning MoM-implants is still very limited. Therefore the comment in the Opinion is justified since it highlights the necessity of additional investigations focussing on

		- Due to the time on the market for the two brands in questions only short term follow-up data are available. The first referenced three HRA brands have been on the market for a longer period. "Most investigations on prosthesis survival do not take into account, however, the potential of local adverse tissue reactions from metal debris, which can arise even in well performing implants." - General comment: Above statement is brought up repeatedly in the report, even when a potential advantage of HRA is mentioned without citing any underlying evidence in relation to HRA. - This may equally be applied to other complications with other bearing combinations for example a survivorship analysis would not identify early osteolysis.	the incidence of local adverse events. No changes to the opinion are required in relation to the comment.
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.3.3. Potential adverse effects (local and systemic) of MoM implants in comparison to non-MoM implants	4.3.3., "Potential adverse effects (local and systemic) of MoM implants in comparison to non-MoM implants", 22 "Nevertheless, it would be good to develop guidelines on the management of patients receiving metal-on-metal arthroplasties suspected of being metal-allergic (Cousen 2012)." - If such guidelines are to be developed by European Orthopaedic Societies, or committees like SCENIHR, it is Eucomed's opinion that consultation and collaboration with industry, as an interested stakeholder, should be sought.	SCENIHR thanks Eucomed for the comment. It is correct that all stakeholders should be consulted. The WG included different stakeholders and an call for information was spread over different communication channels. No changes to the opinion are required in relation to the comment.
Joyce Thomas; Newcastle University; thomas.joyce@ncl.ac.uk; United Kingdom	4.3.3.2. Systemic adverse effects	On pages 26 (and page 11) it is stated that 'it is important to note that wear rate and metal ion release of the historic McKee-Farrar prosthesis are substantially higher than those of modern design MoM implants'. I think there is evidence to suggest otherwise. Tuke et al, 2008, JBJS, 90, Supp III, 134-41, offered wear volumes from 5 explanted first generation metal-on-metal hips (their table 1). Wear rates were 1.1-7mm3/year. These compare with 0.5 to 95.5mm3/year which we have	SCENIHR thanks Joyce Thomas for the comment. See above.

		reported for ASR hip resurfacings (Lord et al, Wear, 2011, 272, 1, 79-87). It should also be appreciated that HR and LHMoM tend to have larger articulating radii than first generation MoM hips. If the HR and LHMoM articulating surfaces roughen and move into boundary lubrication (as shown by Joyce et al, 2009, J Engineering Tribology) then the wear volume per cycle will increase in proportion to the radius. Moreover, first generation MoM hips tended to be monoblock and so lack any concerns over metal release from taper junctions between femoral heads and femoral stems.	
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.3.3.2. Systemic adverse effects	4.3.3.2., "Systemic adverse effects", Systemic toxicity, 24 "Leikin et al (2013) performed an observational study of 39 hip arthroplasty patients (26 of them having MoM THA), who were investigated at two outpatient medical toxicology clinics." - Eucomed would welcome the disclosure by SCENIHR of the selection criteria for including the above referenced study.	SCENIHR thanks Eucomed for the comment. To our knowledge we have included all clinical studies with appropriate methodology in the Opinion, where relevant data for the issue of/on systemic toxicity are reported.
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.3.3.2. Systemic adverse effects	4.3.3.2., "Systemic adverse effects", Systemic toxicity, 24/25 "Two recent investigations systematically looked into potential systemic sequelae of MoM hip arthroplasty (Chen et al 2013, Prentice et al 2013)." - The above referenced studies (n-32 and n=35) are not "systematic", but are considered to be large case series. "There was no evidence of difference in neuropsychological, renal tubular, hepatic or endocrine function between the two cohorts. The authors conclude that chronic exposure to metal concentrations in patients with even well-functioning MoM hip arthroplasty may have systemic effects. - A conclusion of this nature cannot be drawn based on the results of these two small studies.	SCENIHR thanks Eucomed for the comment. The studies looked, using a clear defined methodology (systematic approach) into potential systemic sequelae of MoM hip arthroplasty. The studies themselves can be considered to be large case series. In the second part of the comment a sentence from the Opinion was forgotten "They found an increase of body bone mineral density by 5% and a decrease of bone turnover by 14% in the MoM group. The cardiac ejection fraction was 7% lower (mean absolute difference 25%, P = 0.04) and left ventricular end-diastolic diameter was 6% larger (mean difference 2.7 mm, P = 0.007) in the resurfacing group" Hereafter the cited statement "there was no evidence ….. The authors conclude that chronic

			exposure to metal concentrations in patients with even well-functioning MoM hip arthroplasty may have systemic effects." It is clearly stated in the Opinion that the conclusion was made by the authors of the cited study and not by SCENIHR.
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.3.4. Factors influencing the outcome: surgeon, patient and implant	4.3.4., "Factors influencing the outcome: surgeon, patient and implant", 28 "Several recent studies have shown that the implant per se is influencing the amount of metal particle release and also clinical outcome." - Above statement supports the position that all products should be analyzed individually as there are differences in design, materials and clinical performance.	SCENIHR thanks Eucomed for the comment. Correct, therefore it is advised in the Opinion that patients are strictly followed up.
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.4.1.3. Computed tomography (CT)	4.4.1.3., "Computed tomography", 30 "In the diagnosis of pseudotumours, the sensitivity of CT investigations seems to be comparable to MR imaging (Bosker et al 2012)." ü - Above conclusion cannot be drawn from the referenced article, because it involves MRIs on symptomatic patients.	SCENIHR thanks Eucomed for the comment. This comment is correct; we have changed the opinion accordingly. OLD text: In the diagnosis of pseudotumours, the sensitivity of CT investigations seems to be comparable to MR imaging (Bosker et al 2012) NEW text: Bosker et (2012) could detect pseudotumours in their Patient cohort by CT investigation as well as by MRI Investigation with similar reliability (page 26).
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.4.3. Possibility for analysis of synovial fluid and periprosthetic tissue	4.4.3., "Possibility for analysis of synovial fluid and periproshetic tissue", 32 "The hip joint is the first compartment where metal particles are released. After MoM implantation it is therefore possible to identify	SCENIHR thanks Eucomed for the comment. Correct, measuring metal content needs solubilisation of the particles (resulting in higher metal ion concentration). Therefore it is concluded in 4.4.4. "Measurements of metal particles and/or

		them in the joint fluid as well as in periprosthetic tissue (Beraudi et al 2013, De Pasquale et al 2013, Langton et al 2010, Langton et al 2012, Nadu et al 2012). It is, however, more difficult to retrieve synovial fluid samples or even tissue biopsies than to draw venous blood." - An issue with measuring metal ions based on synovial fluid/tissue biopsies is that single particles can skew data to the high metal ion concentrations contained within those particles.	metal ions in synovial fluid and prosthetic tissue could be helpful in analysing a potential correlation between local metal particle deposition and local or systemic adverse effects. However, appropriate technologies to measure deposited (metallic) particles in tissues are still a subject of research."
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.6.1. Recent opinions and comments	4.6.1. "Recent opinions and comments: Predictive value of metal ion screening", 34 - For information it should be noted that there is an ongoing medical debate regarding the systemic effects of metal ions. The Preliminary Opinion reports that levels of metal ions higher than10 µg/L had a 100% specificity of predicting clinical problems. Analysis reported by Finley, et al., (2) found that biological responses and adverse effects in humans were not observed below measured or estimated blood Co concentration of 300 µg/L. Paustenbach, et a.,l(3) also reported that there is a clear lack of consensus regarding how to identify a specific numerical blood concentration of concern and whether whole blood or serum is a better matrix to assess total cobalt concentration; and concludes that based on currently available data, only under very unusual circumstances should a clinician expect that biologically important systemic adverse effects might occur in implant patients with blood cobalt concentrations less than 300 µg/L. In a study to determine if cobalt and chromium ion levels can predict soft tissue damage at total hip revision, Griffin, et al.,(4) report that using 7 ppb as a threshold, cobalt and chromium ion levels had poor sensitivity and specificity (Co, 65% and 56%; Cr, 29% and 75%). Positive predictive values for cobalt and chromium were only 48% and 26% respectively. The authors conclude that ion levels are unreliable	SCENIHR thanks Eucomed for the comment. It is correct that, as reported by Paustenbach and Finley, systemic effects are rare at blood levels of 300 µg/l Co or less. The levels of 10 (and 7) µg/l blood as a threshold for clinical problems refers to local effect (not systemic) This is also included in the publication of Paustenbach et al 2014: "For example, the UK Medicines and Healthcare Products Regulatory Agency has proposed a blood cobalt guidance value of 7 µg/L, and the Mayo Clinic has suggested serum cobalt concentrations greater than 10 µg/L, but both of these values are primarily intended to address implant wear and to alert physicians to the possibility of an increased incidence of local effects." On page 32, the following text was added: "Paustenbach, et al. (2014) looked into the link between Co-blood levels and systemic effects. They concluded that based on currently available data, only under very unusual circumstances important systemic adverse effects might occur in implant patients with blood cobalt concentrations less than 300 µg/L". This reference is included and discussed in the Opinion. It is also worthwhile to remark (see above) that the determination of metals (ions and/or particles) is still a difficult issue to be resolved.

		predictors of periarticular soft tissue damage and should not be used in isolation as surgical intervention triggers. Eucomed recommends the Scientific Committee considers inclusion of these additional publications within the references of the Preliminary Opinion. References (see attachments): (1) Pamela L. Plouhar, Rodrigo Diaz, Paul Voorhorst. Survivorship of ULTAMET Metal-on Metal Articulation in National Joint Replacement Registries (2) Brent L.Finley, Andrew D. Monnot, Shannon H. Gaffney, Dennis J. Paustenbach DOse-Response Relationships for Blood Cobalt Concentrations and Health Effects: A Review of the Literature and Application of a Biokinetic Model; J-Toxicology and Environmental Health, Part B, 15:493-525, 2012. (3) Dennis J. Paustenbach, David A. Galbraith, and Brent L. Finley Interpreting cobalt blood concentrations in hip implant patients Clinical Toxicology, February 2014, Vol. 52, No. 2, Pages 98-112 4) William L. Griffin Thomas K. Fehring, MD, James C. Kudrna, MD, Robert H. Schmidt, MD, Michael J. Christie, MD, Susan M. Odum, MEd, and Anne C. Dennos, BS, Are Metal Ion Levels a Useful Trigger for Surgical Intervention?, The Journal of Arthroplasty Vol. 27 No. 8 Suppl. 1 September 2012, Pages 32-36. (5) Peltola C., Malmivaara A., Paavola Hip prosthesis introduction and early revision risk. A nationwide population-based study covering 39,125 operations. Acta Orthop. 2013 Feb;84(1):25-31. (6) Lalmohamed A, MacGregor AJ, de Vries F, Leufkens HG, van Staa TP. Patterns of risk of cancer in patients with metal-on-metal hip replacements versus other bearing surface types: a record linkage study between a prospective joint registry and general practice	

		electronic health records in England. PLoS One. 2013 Jul 4;8(7):e65891 (7) Keurentjes JC, Fiocco M, Schreurs BW, Pijls BG, Nouta KA, Nelissen RG. Revision surgery is overestimated in hip replacement. Bone Joint Res. 2012 Oct 1;1(10):258-62	
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.6.1. Recent opinions and comments	4.6.1., "Recent opinions and comments: Predictive value of metal ion screening", 37 "In conclusion, MRI and/or CT are – in addition to conventional radiographs - useful investigations to identify the cause of pain in a symptomatic hip and to support surgical planning." - It is important to monitor over time the progression of the reported symptoms via repeated MRIs (Weegen et al BJJ 2013).	SCENIHR thanks Eucomed for the comment. In 4.6.1 several issues are discussed including repeated investigations, a combination of diagnostic tools and proposed guideline.
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.6.2. European multidisciplinary consensus statement on the use and monitoring of metal-on-metal bearings for THA and HRA	4.6.2., "Safety assessment of patients after implantations of MoM bearings", 37 "If metal ion levels are normal at year one and two postoperatively, the frequency of further annual follow-up investigations may be changed to local protocols for conventional THA." - SCENIHR is invited to define what is meant by "normal".	SCENIHR thanks Eucomed for the comment. "Normal" was not further defined since it depends on the compound considered. As mentioned on p 36, preoperative measurements help to interpret postoperative data. This comment refers to the cited recommendations which have been published in a European multidisciplinary consensus statement (2013).
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.6.2. European multidisciplinary consensus statement on the use and monitoring of metal-on-metal bearings for THA and HRA	4.6.2., "Safety assessment of patients after implantations of MoM bearings", 37 "All patients should undergo radiographic examination during follow-up. In case of clinical / radiographic abnormality, additional imaging (ultrasound, CT-scan, and/or MARS-MRI) is recommended. Ordinary MRI without MARS-technique is ineffective." SCENIHR is invited to: - indicate which data conventional x-ray can provide for this assessment. - clarify if metal ion level is part of clinical assessment during follow-up.	SCENIHR thanks Eucomed for the comment. As already outlined in the Opinion (see chapter 4.4.1.1. on Radiographic imaging) conventional x-ray is helpful to assess component position, and detect potential osteolysis, aseptic loosening or femoral neck fracture. Recommendations about metal ion level assessment during clinical follow-up (including an extensive discussion about the problems of establishing a correlation between metal ion level and adverse

		"In case of Co-values above a certain threshold (within the range of 2 to 7 µg/L;), additional imaging (e.g. ultrasound, CT-scan, and/or MARS-MRI) is recommended." "In increased values above the threshold, additional imaging even in asymptomatic patients is recommended." - There is no scientific evidence which establishes the correlation between metal ion levels and ALVAL.	reactions) are provided in the chapters 4.6.1 and 4.6.2.
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.6.4. Conclusions	4.6.4., "Conclusions", 39 "Currently no universally accepted consensus exists on how patients with implanted MoM arthroplasties are to be managed. It is generally agreed that asymptomatic patients need regular follow-up (time intervals and screening investigations depending on the implant category as well as on the presence of pathologic findings)" - SCENIHR states lifetime follow up for all LHMoM, but there are no underlying scientific data which justify the life-time follow-up of asymptomatic patients.	SCENIHR thanks Eucomed for the comment. It is correct that not much data is available to support this statement. Notwithstanding this SCENIHR considers follow-up as a common good practice for implanted material in general, particularly for those under continuous stress of wear.
Joyce Thomas; Newcastle University; thomas.joyce@ncl.ac.uk; United Kingdom	4.7.1. Risk factors for MoM implants	On page 40 it is stated that one of the specific problems in MoM hip implants is 'large-head THA with trunnion wear due to increased friction'. I feel that use of the term 'friction' may be inappropriate. 'Fretting wear' or 'fretting corrosion' might be better terms to use. We have previously reported data (ref Langton et al, 2012, Bone and Joint Research) from examining 126 retrieved LHMoM components we conclude that the 'primary factor leading to taper failure is the increased lever arm acting on this junction in contemporary large-diameter metal-on-metal hip replacements'. We see increase in head size as being an important explanation as why clinical problems are seen with contemporary large head hips of all types, not just MoM. If it was simply a corrosion problem then why don't we see similar	SCENIHR thanks Joyce Thomas for the comment. The statement in the consensus could have been written more precisely, including all factors, the comment is very helpful! Head diameter increases the friction "moment", which challenges the taper connection: Suggested Change p.40: OLD text: "large-head THA with trunnion wear due to increased friction". NEW text: "large-head THA with trunnion wear due to increased friction moments." (page 37)

		problems with small head MoM hips?	
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.7.3. Follow-up of MoM implants and induced adverse effects	4.7.3., "Follow-up of MoM implants and induced adverse effects", 41 "Concerning follow-up, it is also noted that: - Manufacturers should organize a post-market follow up of their materials on the market." - The medical devices directives require manufacturers to operate a documented Post Market Surveillance system. - In compliance with applicable regulations Eucomed members monitor the clinical performance of their implants including MoM hip implants. - Eucomed recommends that it should become mandatory for hospitals/surgeons to inform manufacturers about any revision of an orthopedic implant including MoM hips and to provide adequate data to enable manufacturers to conduct an investigation into the cause of the reported revision and to decide on whether there is a need for action. Experience shows that hospital/surgeons often do not notify manufacturers about revisions. Data are also often not made available because of potential liability/data protection issues. If these data are not made available to manufacturers, they cannot meet their statutory post market surveillance obligations. - Please see also the recommendation of the IGZ in their report on Metal on Metal hips from May 2013.	SCENIHR thanks Eucomed for the comment. The current applicable regulation is DIRECTIVE 2007/47/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 September 2007amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market. 4.7.3. Follow-up of MoM implants and induced adverse effects: This important aspect is elaborated further in the new proposed Medical Device Regulation (26.9.2012). Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002and Regulation (EC) No 1223/2009.
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.8. Research recommendations	4.8., "Research Recommendations", 42 -Eucomed would recommend to conduct a study into the effects of implant placement/deviations.	SCENIHR thanks Eucomed for the comment. Numerous clinical as well as experimental studies (cited in the Opinion) have been performed to study the effect of different implant positions on wear behaviour, metal ion release and clinical outcome and studies – see chapter 4.3.4.
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org;	4.8. Research recommendations	4.8.3., "Post-market studies", 43 "It is necessary to establish a traceability system in order to follow-up	SCENIHR thanks Eucomed for the comment. This is discussed in the COMMISSION RECOMMENDATION of 5

Belgium		potential adverse events in MoM patients. The infrastructure of partly-existing hip arthroplasty registries in different European countries could be used for this purpose." - SCENIHR is invited to clarify what they mean with a traceability system for the follow-up of potential adverse events in patients. - As mentioned above, applicable regulations require manufacturers to have a system in place to monitor the performance of implants, but for a major part this system relies on the provision of (clinical) data by hospitals/surgeons on the reported revisions. - Joint registers provide data on the reason of the reported revision, but they provide limited data on the actual root cause of subject revision - Registries, while effective at gathering large, typically less detailed datasets, are no substitute for access to individual patient medical records for Post Market Surveillance/Post Market Clinical Follow-up data-gathering.	April 2013 on a common framework for a unique device identification system of medical devices in the Union (2013/172/EU).
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	4.8. Research recommendations	4.8.3., "Post-market studies", 43 "1) Establish Hip Arthroplasty Registers with better documentation of reasons for revision" - There is an urgent need for data standardization and harmonization across the major national and regional arthroplasty registries; so that large data-sets can be pooled consistently with appropriate granularity to allow the detection of rare events that may be early signals of adverse clinical performance. Eucomed recommends that this effort should be coordinated by a suitable independent body, such as but not limited to, the European Arthoplasty Registers (EAR) and/or the International Society of Arthroplasty Registries (ISAR), with collaboration from industry and backed up by necessary legal and regulatory compliance requirements locally.	The SCENHIR members as well as all the external experts are in full agreement with this comment. A recent initiative of EFORT tries to establish a network of European Arthroplasty Registries with a particular focus on improved data exchange.

Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	5. OPINION	5, "Opinion", 45 "Q3: To identify criteria regarding the safety and safe use of MoM implants used in arthroplasty, paying special attention to design and patient groups." - As previously mentioned, special attention should also be given to surgical factors.	SCENIHR thanks Eucomed for the comment. SCENIHR is asked to answer/comment specifically to the Terms of Reference (or ToR, see Heading 3), and these ToR can not be modified. It is correct to mention that surgical factors also play a role; this was also mentioned in the opinion.
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	ABSTRACT	Eucomed, based on input collected from its members who manufacture Metal-on-Metal joint replacements, welcomes the opportunity to provide comments to the European Commission and the Scientific Committee on Emerging Newly Identified Health Risks (SCENIHR)'s preliminary opinion on the safety of Metal-on-Metal joint replacements with a particular focus on hip implants. The SCENIHR's preliminary opinion is a welcome additional step in the ongoing assessment of the safety of Metal-on-Metal joint replacements, with a particular focus on hip implants, as concerns have been raised about the potential impact of metal ion release from large-head metal-on-metal total hip and surface replacement arthroplasty, in particular. General comments Eucomed would like to submit the following general comments: - SCENIHR should analyse the performance of each MoM product individually instead of as a class (>36 or <36mm, HRA) due to the difference in design, materials and clinical performance (see pages 5, 8, 9, 17 and 37); - The categorization per 36 mm head size is arbitrary without sound clinical rationale; - SCENIHR refers to NICE's 90% survivorship at 10 years acceptance criterion. It should be noted that NICE have since revised their guidance (more information available here: http://www.nice.org.uk/newsroom/pressreleases/NICEDraftGuidanceR	SCENIHR thanks Eucomed for the comment. From NICE website: http://www.nice.org.uk/guidance/TA304/chapter/1-Guidance Total hip replacement and resurfacing arthroplasty for end-stage arthritis of the hip (review of technology appraisal guidance 2 and 44) New Guidance NICE technology appraisals [TA304] Published date: February 2014 1. Guidance This guidance replaces NICE technology appraisal guidance 2 issued in April 2000 and NICE technology appraisal guidance 44 in June 2002. 1.1 Prostheses for total hip replacement and resurfacing arthroplasty are recommended as treatment options for people with end-stage arthritis of the hip only if the prostheses have rates (or projected rates) of revision of 5% or less at 10 years.

		ecommendsMoreReliableArtificialJoints.jsp).	
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	ABSTRACT	Abstract, 4 "Local as well as systemic adverse effects can also occur with other types of metallic implants (e.g. plates, screws)". - The above statement is also applicable for other bearing types, e.g. MOP and COC. See Carli A, Reuven A, Zukor DJ, Antoniou J., Bull NYU Hosp Jt Dis. 2011;69 Suppl 1:S47-51, Adverse soft-tissue reactions around non-metal-on-metal total hip arthroplasty - a systematic review of the literature.	SCENIHR thanks Eucomed for the comment. It is correct that other type of implants can give adverse effects; here we only concentrate on metals (ions and/or particles).
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	ABSTRACT	Abstract, 4 Eucomed is aware of clinical follow-up protocols being suggested for patients with metal-on-metal hip implants. They have been developed by regulatory and/or professional societies and independently by surgeon practitioners for their own patients. At this stage, the orthopaedic community has not adopted a universal protocol for asymptomatic or symptomatic patients. Eucomed does not endorse any protocol(s) as being universally acceptable or effective and instead relies on the work of health care professionals, researchers and professional bodies to determine what steps to take post-operatively in any particular case. Eucomed is not in a position to advise any individual practitioner or institution whether a specific clinical protocol must be applied to particular patients or group of patients.	SCENIHR thanks Eucomed for the comment. The comment is a little confusing, on the one hand stating that Eucomed does not endorse any protocol(s) as being universally acceptable or effective and instead relies, etc….. And on the other hand stating that Eucomed is not in a position to advise any individual practitioner or institution. No changes to the opinion are required in relation to the comment.
Sterk Thecla; Eucomed; thecla.sterk@eucomed.org; Belgium	ABSTRACT	Abstract, 5 "The subgroup of large-head MoM implants used in THA should be avoided, on the basis of their high failure risk". - As mentioned in the general comments, performance of each device must be evaluated individually as there exist differences in design, materials and clinical performance	SCENIHR thanks Eucomed for the comment. We agree with the comment, this is in line with the Opinion No changes to the opinion are required in relation to the comment.

German Society for Orthopaedics and Orthopaedic Surgery (DGOOC); Germany. *No agreement to disclose personal data.*	ABSTRACT	A meeting on the subject of Metal-on-Metal joint replacements has recently been performed by the German Society of Orthopaedics and Orthopaedic Surgery in Dresden. The results has been published in Germany and are equivalent to those, which are now published by the European institution. So the DGOOC is completely in agreement with Preliminary Opinion.	SCENIHR thanks the German Society of Orthopaedics for the comment. No changes to the opinion are required in relation to the comment.
German Trauma Society (DGU); office@dgu-online.de; Germany. *No agreement to disclose personal data.*	ABSTRACT	It has been reported by the German Society of Orthopaedics and Orthopaedic Surgery.	SCENIHR thanks the German Trauma Society for the comment. No changes to the opinion are required in relation to the comment.
German Trauma Society; office@dgu-online.de; Germany. *No agreement to disclose personal data.*	ABSTRACT	It has already been reported by the German Society of Orthopedics and Orthopedic Surgery. We support this fully.	SCENIHR thanks the German Trauma Society for the comment. No changes to the opinion are required in relation to the comment.

Comments received via email

Name of individual/organisation	Comment received via email	SCENIHRs Response
Représentation permanente de la France auprès de l'Union Européenne, le Conseiller pour la Sante	 Contributions - French Government .	SCENHIR thanks the French Government for the comment. Most of these concerns have been considered in the main body text, except for the lack of Conclusions in 4.3.3.2. On Page 24, section 4.3.3.2, the following sentence has been deleted: “Until now, the database for these three effects in patients with MoM prosthesis has been small. Due to the complexity of the exposure to the metallic products including particles, ions and still uncharacterized metallo-organic compounds, it is difficult to perform a quantitative estimate of the risk on the basis of ionic blood levels, referring to the toxicological profile of single metals. Metal products released into body fluids are deposited in lymph nodes, bone marrow and internal organs. Therefore it is extremely difficult to define the exact risk of systemic adverse effects.” At the end of section 4.3.3.2, Systemic adverse effects, the following text has been added: "Conclusion: Until now, the database for systemic organ toxicity, carcinogenicity and teratogenicity in patients with MoM prosthesis is still limited. Due to the complexity of the exposure to the metallic products (mainly cobalt and/or chromium) including particles, ions and still uncharacterized metallo-organic compounds, it is difficult to perform a quantitative estimate of the risk on the basis of ionic blood levels, referring to the toxicological profile of single metals. Metal products released into body fluids are deposited in lymph nodes, bone marrow and internal organs. Therefore it is extremely difficult to define the exact risk of systemic adverse effects.