PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	THE CLINICAL IMPLICATIONS OF ELEVATED BLOOD METAL ION CONCENTRATIONS IN ASYMPTOMATIC PATIENTS WITH METAL ON METAL HIP RESURFACINGS
AUTHORS	Langton, David; Sidaginamale, Raghavendra; Joyce, Thomas; Natu, Shonali; Blain, Peter; Jefferson, Robert; Rushton, Stephen; Nargol, Antoni

VERSION 1 - REVIEW

REVIEWER	Pascal-André Vendittoli Professor of surgery Université de Montréal Québec, Canada
REVIEW RETURNED	23-Jun-2012

THE STUDY	Study subject of clear interest, however, primary outcome is not well define and material and method poorly presented.
RESULTS & CONCLUSIONS	Very interesting results but presentation is confuse and inappropriate. Paper should be modified significantly.
REPORTING & ETHICS	Multiple publications on the same subjects. No clear patient flow chart is presented. Impossible to understand patients inclusion / exclusion criterias.

REVIEWER	Olga Huk MD, MSc, FRCS Assistant Professor of Surgery Division of Orthopaedic Surgery McGill University Canada Consultantg (DePuy, Johnson & Johnson)
REVIEW RETURNED	13-Aug-2012

THE STUDY	The publication of this paper may create mass hysteria among orthopaedic surgeons who are following the many patients with resurfacing hip arthroplasties (RHA) and among the patients themselves. All risk factors leading to elevated metal ion levels should be documented. Before this manuscript is accepted for publication, it is essential to complete the data with radiographic analysis of component positioning for this cohort of patients. It is well known that component malposition is an important factor affecting Co/Cr ion levels. In view of the high proportion of females that required revision surgery, and the fact that many of these may have had dysplastic acetabulae, vertical cup positioning in order to achieve adequate host bone contact may have been the cause of higher ion generation. Was there any correlation between cup

	abduction angle and Co ion levels? Given the non-standardized method for blood testing the statistical methods used should be carefully scrutinized my a statistician.
RESULTS & CONCLUSIONS	Cup malposition may be an important factor leading elevated ion levels and this data was not provided.

REVIEWER	Dr Victoria Allgar Senior Lecturer Hull and York Medical School University of York Uniited Kingdom I have no competing interests.
REVIEW RETURNED	12-Sep-2012

THE STUDY	The aim and objectives of the study could be clearer in the paper - the logical place for these would be at the end of the background section. In the text it refers the reader to the "Patient demographics can be seen in table 2." This should be Table 1. There was no analysis to compare the groups based on the classification outlined in Table 2. It was not clear how the difference in the time - mean (range) of 27.3 months (6 - 52) following the initial test - was controlled for in the analysis, as patients will have had the second test at different time intervals. The statistical methods used to investigate the mixed effect modelling of trends in blood Co, would be appropriate e.g. repeated measures, but it was not clear how the data was adjusted for the above time differences. This was because the data was observational rather than a controlled trial with defined follow-up times.
RESULTS & CONCLUSIONS	For the analysis: Mixed effect modelling of trends in blood Co, further detail on the analysis and a table outlining the model would be useful to understand the results. Descriptive analysis of the data would be useful here e.g. means (sd's). Although time since surgery (t=0.966, p=0.3334) was not a significant factor, was this used as a controlling factor for differences in the time until the second test? Was data on the third test analysed? For the event analysis of hip replacement failure analysis, a cox regression model was performed, which is appropriate for the data. The level of blood Co was a positive and significant risk factor - was this based on the initial test result or second test result. A table outlining the cox regression analysis would be useful here, rather than a descriptive summary of the analysis in the text. Table 3 includes the modes of presentation of patients who had a revision. There are a small number in each of the subgroups. Was any analysis undertaken to compare these variables between the groups? Table 4. Predicted probabilities of risk of avoiding revision for patients with different blood Co concentrations 5 and 7 years after initial intervention. There is limited description in the text relating to this table, and how the probabilities were calculated. Was any

	adjustment made for time since surgery, type of device etc? Given the dates for the patient recruitment, how many patients had full 5/7 year follow-up data?
REPORTING & ETHICS	I am unsure if the research ethics have been addressed.
GENERAL COMMENTS	Overall, with the addition of tables outlining the statistical modelling, this paper would be strengthened. Without this, there are some uncertancies regarding the anlayses and the resultant interpretation of the data.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Pascal-André Vendittoli
Study subject of clear interest, however, primary outcome is not well define and material and method poorly presented.
We hope we have emphasised the study aims and the method has been re written in order to make it clearer.
Very interesting results but presentation is confuse and inappropriate. Paper should be modified significantly.
Again we hope we have addressed this in our rewritten methods and results.
Multiple publications on the same subjects.
We are not aware of any publications that examine the clinical course of asymptomatic patients in relation to blood metal ion levels.
No clear patient flow chart is presented. Impossible to understand patients inclusion / exclusion criterias.
We hope that the table we have added addresses this concern.

Reviewer: Olga Huk MD, MSc, FRCS
Consultantg (DePuy, Johnson & Johnson)
The publication of this paper may create mass hysteria among orthopaedic surgeons who are following the many patients with resurfacing hip arthroplasties (RHA) and among the patients themselves.
We cannot address this concern. Unfortunately MoM joints are failing at high rates in many countries. The ASR XL has a 44% failure at 7 years according to the Australian National Joint Registry. This is exactly the figure we predicted in 2010.
All risk factors leading to elevated metal ion levels should be documented. Before this manuscript is accepted for publication, it is essential to complete the data with radiographic analysis of component positioning for this cohort of patients. It is well known that component malposition is an important factor affecting Co/Cr ion levels. In view of the high proportion of females that required revision surgery, and the fact that many of these may have had dysplastic acetabulae, vertical cup positioning in order to achieve adequate host bone contact may have been the cause of higher ion generation. Was there any correlation between cup abduction angle and Co ion levels?
As a group of authors we have written and published on this subject at least four times in the major orthopaedic journals (see below). We have also described the ASR and BHR patients' radiographic and clinical outcomes on multiple occasions. We have shown that this surgeon has comparable technical ability to a number of other well-known surgeons. We do not believe a discussion of cup inclination and anteversion angles is of any benefit here.
Langton DJ, Jameson SS, Joyce TJ, Webb J, Nargol AV. The effect of component size and orientation on the concentration of metal ions after resurfacing arthroplasty of the hip. J Bone Joint Surg [Br] 2008;90-B:1143-51
Langton DJ, Jameson SS, Joyce TJ, et al. Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: a consequence of excess wear. J Bone Joint Surg [Br] 2010;92-B:38-46
Langton DJ, Joyce TJ, Mangat N, et al. Reducing metal ion release following hip resurfacing

arthroplasty. Orthop Clin North Am 2011;42:169-80.
Langton DJ, Joyce TJ, Jameson SS, Lord J, Van Orsouw M, Holland JP, Nargol AV, De Smet KA. Adverse reaction to metal debris following hip resurfacing: the influence of component type, orientation and volumetric wear. J Bone Joint Surg Br. 2011;93:164-71.

Given the non-standardized method for blood testing the statistical methods used should be carefully scrutinized by a statistician.
This has been done as recommended. Professor Rushton is a professor of biological modelling who has 30 years' experience and in excess of 100 publications in modelling complex biological systems of the sort analysed here.
Cup malposition may be an important factor leading elevated ion levels and this data was not provided.
We do not believe this is relevant to interpret the results in this paper. Firstly the ASR prosthesis (resurfacing) has a failure of over 20% in England and Australia at seven years. The ASR THR has an equivalent failure rate of over 40%. This cannot be all poorly positioned implants.

Reviewer: Dr Victoria Allgar

I have no competing interests.

The aim and objectives of the study could be clearer in the paper - the logical place for these would be at the end of the background section.
We have tried to address this as well as possible by re writing the methods and results.
In the text it refers the reader to the "Patient demographics can be seen in table 2." This should be Table 1. There was no analysis to compare the groups based on the classification outlined in Table 2.
Text has been altered as suggested. The patients have been divided into sub sections in table 2 only to show the reader the relative numbers of patients by device in each group. The biological model takes into account device and sex in the analysis and therefore we did not believe that an analysis comparing groups here was necessary.
It was not clear how the difference in the time - mean (range) of 27.3 months (6 - 52) following the initial test - was controlled for in the analysis, as patients will have had the second test at different time intervals.
This is considered in detail in the methodology section for "Mixed Effects Modelling of Trends in Blood Co" and in our further comments below.
The statistical methods used to investigate the mixed effect modelling of trends in blood Co, would be appropriate e.g. repeated measures, but it was not clear how the data was adjusted for the above time differences. This was because the data was observational rather than a controlled trial with defined follow-up times.
We believe that this has been addressed in the paper and in our further comments below.
For the analysis: Mixed effect modelling of trends in blood Co, further detail on the analysis and a table outlining the model would be useful to understand the results. Descriptive analysis of the data would be useful here e.g. means (sd's). Although time since surgery (t=0.966, p=0.3334) was not a significant factor, was this used as a controlling factor for differences in the time until the second test? Was data on the third test analysed?

We have included a fuller description of the results and analysis below:

summary(cobalt_no1_nov1.lme)
Linear mixed-effects model fit by REML
Data: cob2
AIC BIC logLik

1166.737 1203.8 -574.3685

Random effects:
Formula: ~1 | Patient
(Intercept) Residual
StdDev: 1.140969 0.4096451

Correlation Structure: AR(1)
Formula: ~1 | Patient
Parameter estimate(s):
Phi
-0.3386792
Fixed effects: log(Cobalt) ~ Timeop + Sex + Device + Age + Femoral.size

Value Std error DF t value P value
Intercept 1.44306 0.95370 255 1.51311 0.1315
Time since op 0.00042 0.00129 255 0.32911 0.7423
Sex (male) -0.31868 0.16199 255 -1.96718 0.0502
Device (BHR) -0.35208 0.28740 199 -1.22503 0.2220
Age 0.001157 0.00856 255 0.135179 0.8926
Femoral size -0.00549 0.01781 255 -0.30848 0.7580

Correlation:
(Intr) Timeop SexM DvcBHR Age
Timeop -0.028
SexM 0.143 -0.008
DeviceBHR -0.084 -0.110 -0.129
Age -0.449 -0.019 -0.085 0.140
Femoral.size -0.860 -0.023 -0.208 0.006 -0.050

Standardized Within-Group Residuals:

Minimum Quartile 1 Median Quartile 3 Maximum
-3.8746 -0.4086 -0.0188 0.40499 3.2818

Number of Observations: 460
Number of Groups: 201

For the event analysis of hip replacement failure analysis, a cox regression model was performed, which is appropriate for the data. The level of blood Co was a positive and significant risk factor - was this based on the initial test result or second test result. A table outlining the cox regression analysis would be useful here, rather than a descriptive summary of the analysis in the text.
This was based on the first blood result. The analysis was conducted like this following the examination of the change in blood Co over time. We have included the table below however we believe that for the general reader the text is easier to interpret.

Coefficient Exp (coef) Se (coef) z Significance
Sex (male) -0.7761 0.4602 0.3383 -2.294 0.0218
Log (Co) 0.8623 2.3687 0.1022 8.441 < 2e-16
Device (BHR) -2.2215 0.1084 0.6430 -3.455 0.000551

Table 3 includes the modes of presentation of patients who had a revision. There are a small number in each of the subgroups. Was any analysis undertaken to compare these variables between the groups?
This is an excellent suggestion but unfortunately in this paper no we have not. We are examining the differences between these groups in other work in press. Our findings make no difference to the conclusions we have drawn here. While we would have liked to have discussed it in depth here there simply wasn't enough room.
Table 4. Predicted probabilities of risk of avoiding revision for patients with different blood Co concentrations 5 and 7 years after initial intervention. There is limited description in the text relating to this table, and how the probabilities were calculated. Was any adjustment made for time since surgery, type of device etc? Given the dates for the patient recruitment, how many patients had full 5/7 year follow-up data?
We used the outputs from the best fit Cox models identified in the event analysis to generate predicted survival curves for individual patients with the characteristics defined in the text. We then used curves to predict the probability of avoiding the event (revision) at 5 and 7 years with associated CI from the regression equations. In effect they are points on the relevant curves at t=5 and t=7 years with their associated CI .
We state in the paper that every patient underwent minimum of two year follow up post venesection. Table 1 gives the mean time from op to venesection. We state that all BHRs were implanted between 2002 and 2004 so all these patients underwent more than seven year post-operative follow up. The ASRs were implanted between 2004 and Jan 2009 so all ASR patients underwent minimum 3 year post-operative follow up.
I am unsure if the research ethics have been addressed.
This work was carried out as one of clinical need as problems became apparent. Blood metal ion testing is recommended by the MHRA, the FDA and European bodies.
Overall, with the addition of tables outlining the statistical modelling, this paper would be strengthened. Without this, there are some uncertancies regarding the anlayses and the resultant interpretation of the data.
We have tried to include more data in the results to address these issues.

VERSION 2 – REVIEW

REVIEWER	Allgar, Victoria York University, HYMS/Health Sciences
REVIEW RETURNED	17-Dec-2012

- The reviewer completed the checklist but made no further comments.

Correction

Langton DJ, Sidaginamale RP, Joyce TJ, *et al*. The clinical implications of elevated blood metal ion concentrations in asymptomatic patients with MoM hip resurfacings: a cohort study. *BMJ Open* 2013;**3**:e001541.

The funding statement in this article should have been: 'This work was funded by a grant from the British Orthopaedic Association/Joint Action.'

The competing interests statement should have been: DJL, is an unpaid consultant for Wright Medical; DJL, AVFN, SN and TJJ are expert witnesses in ongoing litigation regarding MoM hip joints; DJL has been reimbursed for individual talks for DePuy and Finsbury; AVFN has received reimbursement for DePuy educational sessions; AVFN and DJL have received reimbursement for travel to educational meetings by Smith and Nephew, Zimmer, DePuy and Wright Medical.'

BMJ Open 2013;**3**:e001541corr1. doi:10.1136/bmjopen-2012-001541corr1