



21 May 2011



10 December 2011

Hip implants: how safe is metal on metal?

Deborah Cohen examines the evidence of risk from metal-on-metal hips and how the regulatory bodies failed to protect patients or give them the information they need

This week's *BMJ*/BBC *Newsnight* investigation (www.bbc.co/iplayer) on the safety of metal-on-metal implants follows our coverage last year of the now withdrawn DePuy ASR device. Then we focused on the less than stringent regulatory environment and the commercial vested interests that together delayed the recall of this failed prosthesis from the market. This week Deborah Cohen takes the story on, drawing together evidence that hundreds and thousands of patients may have been exposed to toxic substances after being implanted with potentially dangerous hip implants, which are still on the market. Carl Heneghan and colleagues (p 23) examine in detail what has gone wrong with metal-on-metal implants.

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- News: UK medical device regulation is criticised as both cumbersome and inadequate (*BMJ* 2012;344:e1202)
- Practice: Diagnosing and investigating adverse reactions in metal on metal hip implants (*BMJ* 2011;343:d7441)
- Research: Comparative assessment of implantable hip devices with different bearing surfaces: systematic appraisal of evidence (*BMJ* 2011;343:d7434)
- Feature: Europeans are left to their own devices (*BMJ* 2011;342:d2748)
- Feature: Out of joint: the story of the ASR (*BMJ* 2011;342:d2905)

Hundreds of thousands of patients around the world may have been exposed to toxic substances after being implanted with poorly regulated and potentially dangerous hip devices, a *BMJ*/BBC *Newsnight* investigation reveals this week. Despite the fact that these risks have been known and well documented for decades, patients have been kept in the dark about their participation in what has effectively been a large uncontrolled experiment.

This isn't the unlucky failure to spot the misdemeanours of one rogue company or the occasional unforeseen breakdown of a small number of devices. It is the inability to prevent a whole class of failing hip implant from being used in hundreds of thousands of people globally—a class of implant that the usually reticent National Joint Registry of England and Wales described recently as a “cause for concern.”^{1 2} The implants concerned are “metal on metal”—the head at the top and the lining of the cup it fits into are made of cobalt-chromium alloy rather than ceramic or polyethylene—and there are models for both total hip replacement and hip resurfacing.

From their arrival on the orthopaedic scene in 1997, they were marketed as the latest advance in hip replacement and were targeted at young active patients who needed a hip that would last a whole lifetime. And while there is evidence that hip resurfacing works well in young active men,³ the failure rates of resurfacing in women and of metal-on-metal total hip replacements in both sexes are higher than they should be. Average failure rates at seven years are 11.8% for resurfacing and 13.6% for metal-on-metal total hip replacement, although failure rates vary with the brand used. This compares with rates of 3.3%–4.9% for hip implants made of other materials.²

Metal-on-metal devices have been implanted into over 60 000 patients in England and Wales since 2003—when the National Joint Registry first began to record procedures. Before this date numbers are unreliable. In the US the figure is closer to a million and likely to increase. At the annual American Academy of Orthopedic Surgeons con-

ference in February this year, a roll call of manufacturers was still promoting these products to the 40 000 attendees in the exhibitor hall.

Cobalt-chromium implants have been used successfully in orthopaedics for years—for example, in knee operations and fracture repair. They are known to release metal ions, but some metal-on-metal prostheses do so on a much greater scale than previously thought. These ions can seep into local tissue causing reactions that destroy muscle and bone and leaving some patients with long term disability.⁴ Local tissue reactions associated with ions from metal-on-metal hips were first described in detail as long ago as 1975.⁵ The ions can also leach into the bloodstream spreading to the lymph nodes, spleen, liver, and kidneys before being excreted in urine.⁶

Metal ions and genotoxicity

Multiple studies and research organisations have warned about the carcinogenic potential of metal-on-metal hips.⁷ That cobalt and chromium ions lead to genotoxic changes both in laboratory settings and in animals was described in scientific journals over 30 years ago.⁸ Cobalt too was shown to be linked to cardiomyopathy in 1966.⁹ However, the link to cancer is not proved.

In 1990, the World Health Organization International Agency for the Research on Cancer released a monograph listing hexavalent chromium as a proved carcinogen; trivalent chromium a potential carcinogen; and cobalt ions a probable carcinogen.¹⁰

Only recently—after the early failure of thousands of implants—have tests from the London Implant Retrieval Centre, a centre that tests prostheses, confirmed that trivalent chromium is the ion being released.¹¹

The manufacturers were aware of the potential for genotoxicity. The *BMJ* and *Newsnight* have seen a DePuy internal memo from July 2005 that says: “In addition to inducing potential changes in immune function, there has been concern for some time that wear debris may be carcinogenic. The mechanism is not known and only 24 local malignancies have been reported in patients with



Large diameter metal-on-metal hip implant highlighting wear pattern caused by toggling on models with short tapers



Chris Bulstrode, orthopaedic surgeon, Oxford University, tried to warn the Department of Health about overzealous innovation. “There was no interest in blocking British inventiveness”



Cobalt-chromium implants can release metal ions. These can seep into local tissue causing reactions that destroy muscle and bone and leaving some patients with long term disability



Nick Freemantle, professor of clinical epidemiology: “We shouldn’t be in this position where there’s so much uncertainty”

joint replacements. Also worrying is the possibility of distant effects. One study suggested a threefold risk of lymphoma and leukaemia 10 years after joint replacement. The metal to metal total hip appears to be quite promising and in the laboratory the data is (sic) definitely in its favour. However, the ultimate test is the long term human experience.”

Despite this uncertainty, DePuy’s marketing of metal-on-metal hips continued unabated, with promotional material failing to reflect internal company concerns. Instead, in 2006 the sales teams were equipped with a paper entitled “Setting the record straight on metal hypersensitivity,” written by one of DePuy’s prosthesis designers, Los Angeles orthopaedic surgeon Thomas Schmalzried, to counter emerging concerns on the topic.

Meanwhile the UK’s Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment started to have concerns about the carcinogenic potential of metal-on-metal hip implants.¹² In response, the Medicines and Healthcare Products Regulatory Agency (MHRA) convened a meeting in March 2006 to discuss the long term health effects.

The agency knew this was a sensitive topic. The minutes describe how the chairman stressed

the importance of confidentiality before the paper was presented and that “anyone who felt they were unable to keep this matter completely confidential was asked to leave the room.” No one left.¹²

The MHRA discussed the problem with the Department of Health’s Committee on Mutagenicity. In July that year (2006), the committee concluded that “there is evidence to suggest that some metal-on-metal (those using cobalt-chromium) hip replacements may be associated with increased DNA-changes, and increased genotoxicity in patients.” It said this “gave rise to concern because this may present a potential risk of carcinogenicity in humans.”¹³ But it concluded that the clinical implications were uncertain.

To try to establish the risks posed by metal-on-metal implants, the MHRA subsequently appointed an expert advisory group. Of the group’s eight members, three had conflicts of interest: two were DePuy consultants and one was the director of product development for Smith and Nephew. The group’s brief was to put metal hips “into a risk-benefit context.” There was no statistician or epidemiologist in the group.

In the face of such hazard and uncertainty, the group could have warned against the use of metal-on-metal hips, which had not been shown

in comparative trials to be better than conventional hips. According to the minutes of the first meeting in October 2006, Patrick Case, a senior lecturer in orthopaedic surgery and pathology, said: “Surgeons have a choice of which [prosthesis] to implant.”¹⁴ Instead, the minutes highlighted the benefits of metal-on-metal implants for resurfacing and total hip replacement. The group did not heed the advice of Derek McMinn, designer of Smith and Nephew’s Birmingham Hip Resurfacing (BHR) implant. He had published a paper in the UK’s main orthopaedics journal, the *Journal of Bone and Joint Surgery*, in 2004 concluding: “Caution still needs to be exercised until longer term results are available.”³

Nor did it choose to contraindicate metal-on-metal hips in women of childbearing age—even though metal ions had been detected in umbilical cord and placental blood. Instead the group criticised the US Food and Drug Administration, which had contraindicated this use, for an unclear risk analysis.¹⁵

As a result of the group’s advice, the MHRA’s Committee on Safety of Devices concluded in July 2007 that patients should sign a consent form “which sets out the fact that the risks associated with metal wear debris have been discussed, including the genotoxic risk and pos-

HOW COMMERCIALISM TRUMPED SAFETY

Why are patients still exposed to the harms of metal implant failures identified in 1975— implants that divided the orthopaedic community when they were reinvigorated in the 1990s?

The answer seems to be unfettered innovation coupled with a drive for commercial success unconcerned with patient safety.

The conventional total hip replacement consists of a metal head with a polyethylene cup. But these joints don’t last forever. Over time the plastic cup wears away against the hard metal head. Younger, more active people are especially likely

to require early revision surgery to replace the worn out joint.³²

Through the 1960s and ’70s, surgeons were looking at ways to preserve more bone. After a failed attempt in 1970 to develop the resurfacing technique with metal on polyethylene, attention turned to metal as a more durable option. In particular, a combination of cobalt and chromium—the same metals that had given rise to concerns when used in total hip implants in the 1970s.

Birmingham surgeon Derek McMinn took to his garden shed to design a resurfacing prosthesis made of metal. If done correctly—

carefully—he believed an implant could be made with metal surfaces that did not touch and surfaces that wore very little.

Once it hit the European market in 1997, the Birmingham Hip Resurfacing—acquired by Smith and Nephew—rapidly gained popularity as it preserved more bone, was believed to last a lifetime, and virtually eliminated the risk of dislocation, allowing patients to get back to heavy jobs and playing sport.³

But the initial release of the BHR onto the market was tightly controlled. Mr McMinn, the designer,

personally instructed selected surgeons and emphasised the need for good surgical technique and patient selection.

The positive results—lower wear, less risk of osteolysis, and less dislocation—soon piqued the interest of other manufacturers keen to be part of the metal revolution.¹⁷

But as the excitement over hip resurfacing grew through the early 2000s, surgeons continued to report the bodily spread of metal ions released through the wear of implants.³³ The reinvigorated metal technology was controversial and the risks were too high for some.

sible sequelae.” The committee wanted to “ensure patients know there is a risk now and sign consent if necessary,” minutes say.¹⁶

But this requirement was not communicated widely—no alert was put out to surgeons or patients.

According to Tony Nargol, an orthopaedic surgeon at University Hospital of North Tees, surgeons were unaware of these discussions.

Data that the National Joint Registry supplied to the *BMJ* show implantation rates peaked in the following two years, and over 20 000 large diameter metal-on-metal hips alone were implanted thereafter.

Only in March 2011 did the British Orthopaedic Association warn that large diameter metal-on-metal total hip replacements should be “carefully considered and possibly avoided.”¹⁷

Nor did the MHRA require companies to start proper post-approval studies. Although epidemiological studies have not found a link with cancer,¹⁸ they may not reflect the current reality. The metal hips currently being implanted are different in design from earlier models on which the studies were based, and since metal on metal has primarily been used in younger people, patient demographics have also changed. The *BMJ* is aware of one UK case series that is due to report next month.

Uncertain risks from metal ions

Uncertainty surrounds the toxicology of metal ions in the body. As a commentary in the *Lancet* in

2007 said: “Little is known about the transport, distribution, and excretion of metal ions in the body,” adding, “Toxic effect thresholds have not been characterised.”¹⁹

Nick Freemantle, professor of clinical epidemiology and biostatistics at University College London, suggests this level of uncertainty would not be acceptable in drug regulation. “If it was the pharmaceutical industry developing a new chemical entity, it would be abandoned early on if it metabolised in the wrong bits of the liver,” Professor Freemantle says. “We shouldn’t be in this position where we don’t know and there’s so much uncertainty. The stability of a compound should have been ascertained before it was used widely in people. As yet, we don’t know the consequences of this.”

There are no guidelines on what constitutes an unacceptably high level of cobalt ions in blood for patients receiving orthopaedic implants.¹⁹ DePuy’s designer and consultant, Dr Schmalzried, has said that, in patients with a well functioning device, levels should be no higher than 2 µg/L.²⁰ However, he may have seen this as a marker for device failure rather than in relation to safe levels of metal ions in the patient’s blood.

In fact, studies show that blood cobalt concentrations generated through the wear of some of the newer metal-on-metal total hip prostheses can reach over 300 µg/L—higher than anything routinely documented in the past. This is 600 times higher than physiological levels of cobalt—most healthy people have about 0.5 µg/L of cobalt

in their blood.²¹ According to the MHRA, patients should be investigated above a threshold level of 7 µg/L,²² although it is unclear what this figure is based on or how it was derived.

Metal ion levels above this level have been recorded in around 20% of patients (range 5-22%) with some metal-on-metal prostheses—such as DePuy’s flagship Pinnacle hip system.²³⁻²⁵ Over 300 000 Pinnacle prostheses have been put in worldwide.

Data showing raised metal ions in people with the Pinnacle have been available in the medical literature since 2008,²³ yet the device formed a key part of DePuy’s main hip strategy in 2009, as internal emails show. Pinnacle was promoted as “an alternative for the majority of patients” when the ASR implants were recalled globally in 2010. The Pinnacle is not the only metal-on-metal implant causing increased metal ion concentrations. A two year follow-up study published in May 2011 shows an incremental increase in metal levels in 144 patients with large head metal-on-metal implants made by companies including Zimmer, DePuy, and Smith and Nephew.²⁶ Other studies have shown raised ions with Smith and Nephew’s Birmingham total hip replacement (range 1.2-14.2 µg/L, 20% > 7 µg/L),²⁷ Zimmer’s Durom total hip replacement (range 1-12 µg/L),²⁸ and ASR-XL total hip replacement (0.7-217 µg/L).²⁹

Also problematic are the smaller hip resurfacing implants, which are used in women and smaller men. Because these implants lubricate

Timeline: Metal-on-metal hips

1975
Study describes local tissue reactions caused by cobalt and chromium ions from metal-on-metal hips⁶

1991
First metal-on-metal hip resurfacing device is implanted in Birmingham



1988
Study shows human synoviocytes killed by cobalt in vitro (Rae T. *Clin Orthop* 1988;232:244-54)

1994
Study shows dissemination of cobalt and chromium ions into lymph, liver, and spleen⁵

1989
Metal-on-metal hip resurfacing designs start in Birmingham

1996
Patients with metal-on-metal hips found to be at increased risk of cancer compared with those with metal-on-plastic hips: relative risk of haematopoietic cancer 1.59 (95% confidence interval 0.8 to 2.8) and leukaemia 3.77 (0.9 to 17.6) (Visuri T, et al. *Clin Orthop* 1996;329 (suppl):S280-9)

1997
Birmingham Hip Resurfacing (BHR) implant comes onto the European market (left)

1998
Particles of cobalt and chromium shown to be toxic to monocytes in culture (Haynes DR, et al. *Clin Orthop* 1998;352:223-30)

2000
NICE guidance on selection of prostheses for primary hip replacement and resurfacing sets a benchmark revision rate for conventional hip replacement of <10% at 10 years

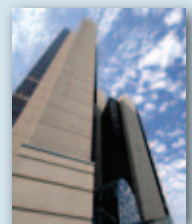
2003
Derek McMinn and Ronan Treacy publish paper showing positive results with BHR. This kickstarts the trend for larger heads in total hip replacement

2004
McMinn, designer of the BHR, says, “Caution still needs to be exercised until longer term results are available”
One of DePuy’s modified stems with a shortened trunnion is cleared by the FDA, which says the modified design “does not raise any new issues of safety or effectiveness”



2005
Internal DePuy memo reflects early concerns about health risks of wear debris from metal-on-metal hips. “In addition to inducing potential changes in immune function, there has been concern for some time that wear debris may be carcinogenic”

2006
MHRA Committee on Safety of Devices says there’s growing concern over the biological risks of metal wear debris



The Department of Health’s Committee on Mutagenicity concludes that “some metal on metal (those using cobalt-chromium) hip replacements may be associated with increased DNA-changes, and increased genotoxicity in patients.” It says this “may present a potential risk of carcinogenicity in humans”

less well, they produce metal debris and high metal concentrations in the blood. In the largest published series, 5% of 343 people, and 17.8% of those with a small Birmingham hip resurfacing, were found to have blood cobalt concentrations above 7µg/L.³⁰

Tweaking the design

Instead of alerting regulators and patients to their concerns, companies tweaked the design of their total hip implants. In 2004, in an effort to rationalise their product range and increase usage of their implants, they shortened the trunnion (or taper)—the part of the stem that inserts into the head—to allow a few degrees greater motion and added grooves so surgeons could use them with both ceramic and metal heads.

A recent Zimmer advertisement for the Spotorno stem, used as part of a metal-on-metal total hip replacement, describes design modifications to the stem. “In order to increase the range of motion and reduce impingement, the length of the taper has been shortened and the neck diameter has been reduced,” it says.

But these changes, coupled with bigger and bigger heads, had unforeseen consequences: increased wear, high levels of metal ions in the tissues and blood, and higher rates of joint failure. Even a small change in design can have a substantial effect on long term outcome, as teams from Newcastle University and the London Implant Retrieval Centre have found. Using a complex algorithm on a coordinate measuring machine,

they have measured the wear of these metal heads to see how damaged they become.

“We think that over the years these taper connections have just become shorter and shorter at the same time as the heads have become bigger and bigger. And we believe, it’s just a leverage effect that’s causing toggling and the joint to wobble,” says Tom Joyce, a biomedical engineer specialising in the design and evaluation of artificial joints at Newcastle University.

They found that where the head joins the stem, the inside becomes blackened because the metal has worn away. The amounts are tiny—equivalent to a pinhead. But the consequences can be devastating. “We’re seeing patients with tapers which are blackened, destroyed, metal getting into the tissues of the hip, damaging the muscles, taking out some of the bone, so destroying parts of the pelvis,” Mr Nargol says.

He adds that surgeons were unaware of the changes when companies implemented them. Indeed, some new implants by Zimmer and DePuy were marketed on the fact that their stems had remained unchanged over time using data from the previous unmodified model.

Far from being confined to a few prostheses, such risky design tweaks seem to be industry wide and on a scale that may be far greater than previously reported. And it seems that industry leaders are fully aware of the scale of issue. In a June 2010 internal email seen by the *BMJ*, a senior figure in DePuy writes: “I feel the problem [with large diameter metal on metal] is emerging as

more serious than first thought.” DePuy had been contacted in 2009 by Japanese surgeons with concerns about the Pinnacle metal hip system, as an internal DePuy email shows. The surgeons reported seeing “generated metal debris between stem taper and head, and final necrosed tissue” and blamed it on the poor connection between the two.

Perhaps most worryingly, DePuy’s senior engineers were still trying to figure out why the implants were failing in 2010—over five years after the design changes had occurred. DePuy enlisted the help of Southampton University to conduct an in-depth investigation. But they did not tell surgeons to stop using their product while they investigated the matter.

Regulatory failure

As for the regulators in Europe and the US, they failed to identify the design changes and their consequences for patient safety. “It’s intrinsically tricky to know when you have a different device. Regulators find this very difficult to spot. But it can’t be the decision of the manufacturer when they need more scrutiny,” says Professor Freemantle. Indeed, the shortening of one of DePuy’s trunnions was cleared by the FDA in December 2004 with the comment: “The design, while not identical to the predicates, does not raise any new issues of safety or effectiveness.”³¹

The MHRA was first made aware of the problems in 2011, through emails



2007

Implantation of large diameter metal-on-metal hips starts to increase rapidly in the UK, and resurfacing peaks. Metal-on-metal hips account for 20% of market this year

UK expert advisory group chooses not to contraindicate metal-on-metal hips in women of childbearing age—even though metal ions had been detected in the umbilical cord and placental blood

The MHRA’s Committee on Safety of Devices recommends that all patients sign a consent form setting out the risks associated with metal wear debris. But this recommendation is not widely communicated



2008

Study shows 20% of patients with DePuy’s Pinnacle hip system have metal ion levels over the upper limit accepted by occupational health experts

2009

Japanese surgeons raise concerns with the design of DePuy’s large diameter metal-on-metal system. They report seeing “generated metal debris between stem taper and head, and final necrosed tissue” and blame it on the poor connection between the two

All joint replacement implants are re-classified as class III devices after the implementation of Directive 2005/50/EC

2010

In an internal email obtained by the *BMJ*, a senior figure in DePuy writes: “I feel the problem [with large diameter metal on metal] is emerging as more serious than first thought.”

DePuy recalls its ASR hip prostheses. Some studies show a failure of the total hip replacement secondary to adverse reactions to metal debris of 50% at 6 years

DePuy promotes Pinnacle—including metal on metal—as “an alternative for the majority of patients”



2011

Tony Nargol and his team warn the MHRA of failures with the Pinnacle implants

British Orthopaedic Association writes to surgeons to say that large diameter metal-on-metal total hip replacements should be “carefully considered and possibly avoided”

A two year follow-up study in 144 patients shows an incremental increase in metal levels over the study period in a range of large head metal-on-metal implants made by companies including Zimmer, DePuy, and Smith and Nephew²⁶



FDA writes to about 20 manufacturers to say that it is requiring post-marketing studies in cases where an implant’s failure could have serious consequences. Companies would be expected to take blood samples from patients to measure metal ions.

National Joint Registry describes large diameter metal-on-metal and resurfacing prostheses in some people as a “cause for concern”

Trial comparing large diameter Birmingham hip replacement with conventional hip is terminated after 2 years. Metal ion levels were raised above the MHRA advised safety level (7 µg/L) in 20% of the metal-on-metal group and in one patient in metal-on-polyethylene group (who had a metal-on-metal implant on the contralateral side)²⁷

2012

At the annual American Academy of Orthopedic Surgeons conference manufacturers promote metal-on-metal products to the 40 000 attendees

REGULATORY ROLE OF EUROPE'S "NOTIFIED BODIES"

DePuy's Pinnacle large diameter metal-on-metal implants obtained certificates of safety and performance in 2009 and 2010 despite the emerging concerns. This enabled the Pinnacle to display a CE mark and be sold in Europe.

To get the CE mark, DePuy turned to the British company BSI, one of several so called "notified bodies" that assess devices for European regulation. Internal documents show that regulatory managers in DePuy UK believed they had a good working relationship with BSI—although they said in 2008 that BSI was asking tougher questions. Nevertheless, unlike in the US, European regulation

doesn't require clinical trials even for the highest risk device class, which hip implants now fall under. It is unclear to what extent BSI took account of concerns about basic design flaws and metal toxicity, all of which were well known to DePuy. The *BMJ* asked BSI if it knew of these concerns when it approved the Pinnacle implant. It declined to comment, saying it was "bound by strict obligations of confidentiality to our clients."

Meanwhile MHRA chief executive Kent Woods (pictured) said publicly on 17 February 2012 on BBC Radio 4's flagship news programme, *Today*, that he has faith in the notified bodies. Others are less sanguine. Peter



McCulloch, a reader in surgery at Oxford University, says there are potential hazards in the current system. "The EU system of approval by agreement between manufacturer and a commercial regulatory body, under conditions of almost total commercial secrecy, overseen in a 'hands off' manner by national regulatory authorities, seems extraordinary in its lack of transparency and the obvious inherent risks of collusion," he says.

from Mr Nargol. The agency asked for more information. "Clearly you have an issue with the DePuy taper, but you have said this is a generic problem across orthopaedics and that many companies changed their trunion (sic) design around 2005. Could you point us towards any of the other implants that have had these trunion (sic) changes so that we know which ones to look at?"

But regulatory failure started much earlier than this. When the devices were launched in Europe in 1997 directives placed hip implants into a category of device that required only simulator testing—a process that puts the hip through cycles of mechanical testing—which even DePuy acknowledged at the time was not the "ultimate" test.

"The fact that the entire system is based on device safety and functionality, with no efficacy requirement is also very surprising when it is applied to invasive treatment technology with significant inherent risk potential," says Peter McCulloch, a reader in surgery at Oxford University.

In the US, the FDA considered the parts of metal-on-metal total hip replacements to be like other heads, cups, and stems already in use. This meant that the devices could be cleared through a less rigorous process, called 510(k), which requires no clinical studies to show how well these large heads worked when coupled with a modified stem.

"This is one very large uncontrolled experiment exposing millions of patients to an unknown risk. We will only find out about the safety of these devices after large numbers of people have already been exposed," says Michael Carome, deputy director of Public Citizen's Health Research Group, a US not for profit consumer advocacy group.

The FDA started to clear larger heads for market

use in 1998 and by the end of 2010 had approved 175 implants through the 510(k) route. And so a whole new class of implant—with the potential to release high concentrations of toxic ions—was launched onto the US and European markets without the need to conduct clinical trials and without any long term post-marketing studies.

But resurfacing was a new technique and so, in the US at least, the implants had to go through the FDA's more rigorous premarket approval process. This requires manufacturers to submit their product to clinical testing to prove it is both safe and—unlike the European process—effective for its intended use. It was this premarketing approval process that stopped DePuy's failing ASR resurfacing prosthesis coming to market,¹⁷ although the ASR XL total hip replacement was passed through the 510(k) route. An international product manager for DePuy responded to similarly lax regulation in South Africa with an email to colleagues in June 2007 saying, "You could literally implant a tent rod if you wanted!"

Clinical trials achieved some changes of heart. A 2011 trial comparing large diameter metal-on-metal with conventional hip replacements made by Smith and Nephew was stopped after two years as 20% of patients in the metal-on-metal group had raised metal ion concentrations in the blood.²⁷

However, such data had little effect on patient safety. According to Chris Bulstrode, an orthopaedic surgeon at Oxford University, when he tried to warn the Department of Health about overzealous innovation, there was no appetite for determining effectiveness in trials. At a meeting with the implants division of the Department of Health in the early 1990s, Mr Bulstrode maintains the director didn't want to hear of problems. "There was no interest in blocking good British

inventiveness, and there were no techniques apart from careful and prolonged follow-up to find out if these implants were better than the well-proven Charnley. It would have taken a minimum of 10 years and no one had time for that when marketing departments were buying for new product," he said.

Post-marketing surveillance

That the high levels of metal ions produced by the modified devices were not picked up by either the European or American regulators on market entry is a cause for concern. So too is the fact that the regulators mandated no post-approval studies requiring careful follow-up of patients implanted with devices capable of producing toxic debris. Instead, the only follow-up data came from ad hoc studies by individual research teams.

The FDA has now decided to gather and review all available information about currently marketed metal-on-metal hip systems, including information related to adverse events that may be associated with increased levels of cobalt and chromium in the bloodstream.³⁵

To that end in May 2011 the FDA wrote to about 20 manufacturers to say that it was invoking a rule requiring post-marketing studies in cases where an implant's failure could have serious consequences. Companies would be expected to take blood samples from patients to measure metal ions. They are also taking a decision on the classification of hip prostheses and how they should be regulated in future. In response to this investigation, the MHRA this week issued emergency guidance for routine monitoring of patients' ion levels. According to meeting minutes it is trying to link up the NJR with the National Cancer Registry. But experts argue this is no proxy for post-marketing surveillance.¹⁸

Conclusion

After a series of failures, device regulation is in need of radical change. For its part, the FDA has decided to place all hip implants into a high risk category—fast track entry will be forbidden.

In Europe there is little doubt the current system is not fit for purpose and talks are under way about how to improve it. As Professor Freemantle asks: "Why is it that people are afforded different levels of protection depending on whether they have a heart attack, diabetes, or a hip replacement in their old age? The methods of device regulation seem to be more from the 1950s than the 21st century."

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Competing interests: None declared.

Provenance and peer review: Commissioned; externally peer reviewed.

References are in the version on bmj.com.

Cite this as: *BMJ* 2012;344:e1410

COMMENTARY **Carl Heneghan, David Langton, and M Thompson**

Ongoing problems with metal-on-metal hip implants

Major advances in total hip replacement have occurred since the prosthesis was first developed by Charnley in the 1960s. Yet substantial concerns currently exist over newer hip implants as a result of rising revision rates and increased risk of cancer.

By the 1980s revision rates of total hip replacements were as low as 20% after 15 years of follow-up.¹ Throughout this era, the main focus was reducing aseptic loosening and osteolysis, which were thought to reduce lifespan. Various combinations of materials have been used in attempts to improve the lifespan of prostheses, which comprise three main types: metal on plastic, metal on metal, and ceramic on ceramic. The first word in the name refers to the head and the second name the cup (metal on plastic is a metal femoral head against a plastic acetabular cup).

Hip resurfacing systems use metal to replace the surface of both joints, preserving the femoral head. Conventional total hip replacement requires complete removal of the femoral head with the prosthesis secured into the upper part of the femoral shaft. Hip resurfacing became popular for younger patients, in whom a quicker return to function and a more active lifestyle are priorities,² but it is a challenging operation requiring specialised training and practice.³

In 2000, the National Institute for Health and Clinical Excellence (NICE) guidance on selection of prostheses for primary hip replacement and resurfacing set a benchmark revision rate for conventional hip replacement of 10% or less at 10 years.⁴ At the time NICE stated, "Surgeons should ensure that patients considering MoM [metal-on-metal] hips resurfacing arthroplasty understand that less is known about the medium-to-long term safety and reliability of these devices or the likely outcome of revision surgery than for conventional hip replacements."⁵

However, over a decade later, evidence on safety is still lacking. A 2011 systematic review of 29 studies of hip resurfacing found no studies fulfilled the NICE 10 year benchmark of 10%.⁶ Indeed, a 2007 technology assessment of hip resurfacing concluded "the peer-reviewed literature had not kept pace with changes in hip resurfacing technology."⁷

Problems with hip devices emerged in July 2008 when the Zimmer Durom acetabular component was voluntarily recalled because of much higher failure rate than expected. And in 2010 DePuy had to voluntarily recall its ASR hip prostheses (one for resurfacing and one for total hip replacement) because of failure rates of about one in eight.⁸ A year later the UK regulator, the Medicines and Healthcare Products Regulatory Agency (MHRA), had to send letters to surgeons to notify them "that some of the 40 000 patients who received the metal-on-metal DePuy ASR hip implants never received the recall notice."⁹ At the British Orthopaedic Association's 2011 conference, further concern was expressed that large diameter metal-on-metal devices from other manufacturers were also showing higher than expected failure rates, especially in women.¹⁰ To add to all this, complaints of "metal poisoning" are growing among patients with DePuy Pinnacle metal-on-metal hip implants.

Metal erosion

Metal-on-metal hip components are constructed from a cobalt-chromium alloy. The levels of these ions increase in the body after implantation and seem to persist in some patients, particularly those whose implants suffer wear

and tear. The potential health hazards of these metals are well known and limits are placed on workplace exposure. The Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) provides threshold values that are regularly updated.^{11 12} In 2006, the UK exposure equivalents of carcinogenic substances (EKA values) corresponding to the workplace exposure limits were 5.0 µg/L in whole blood for cobalt and 17 µg/L in erythrocytes for chromium.¹³ Yet in a cohort of 426 patients with an ASR implant, 28% (and 41% of women) were found to have cobalt levels above 5.0 µg/L.¹⁴ Median chromium and cobalt concentrations in 111 patients with the Birmingham (BHR) hip replacement had increased to 5.1 and 4.3 µg/L, respectively, just two years after surgery.¹⁵

Concerns over levels of cobalt and chromium found in patients with metallic hip replacements were first raised over 40 years ago.¹⁶ Large diameter metal-on-metal bearings result in a greater systemic exposure of cobalt and chromium ions.¹⁷ In addition, chromosomal aberration rates in blood and bone marrow samples are higher in cells adjacent to the prosthesis at the time of revision.¹⁸

Although several cohort studies have found no increased risk of cancer after total hip replacement,^{19 20} a recent retrospective study of causes of death found patients with metal-on-metal hips had higher cancer mortality than patients with metal-on-polyethylene during the first 20 years after implantation but not thereafter.²¹ Temporary increases in haematopoietic cancers at different follow-up periods have also been observed, as well as small increases

A recent retrospective study of causes of death found patients with metal-on-metal hips had higher cancer mortality than patients with metal-on-polyethylene during the first 20 years after implantation but not thereafter



Metals debris that has been removed from the tissue surrounding a metal-on-metal hip implant, DePuy's ASR-XL device (centre), Tony Nargol and team

in prostate cancer and malignant melanoma.²² However, mean follow-up in studies tends to be short and the exposure level is shifting, pointing to the need for continued vigilance.²³ A safe level for metal ions has yet to be defined for patients with hip implants.²⁴

Side effects of cobalt toxicity were also noted 40 years ago and include nausea, vomiting, nerve damage, and thyroid and cardiovascular disorders.^{25,26} Epidemiological studies of workers have established that inhaled chromium increases the risk of lung cancer. Chromium can also cause problems with the reproductive system; indeed, the US Food and Drug Administration states metal-on-metal prostheses should not be implanted in women of child bearing age.²⁷ Raised cobalt levels have been found in newborns of mothers with such hips.^{23,28}

Design flaws

The ASR total hip implant has now been shown to have a failure rate of up to 50% within six years.¹⁴ There are two main reasons for this. The first, which is ASR specific, is that the design of the cup is too shallow. Metal-on-metal joints are designed to harness naturally occurring lubricating fluids from the native hip. In a shallow joint the prosthetic head has a greater tendency to rub against the edges of the cup. This starves the joint of lubrication and greatly accelerates wear. As wear debris is generated, hip joints become filled with high concentrations of chromium and cobalt. This leads to a chain of events culminating in extensive soft tissue necrosis and disruption of bone. The metallic ions then diffuse into the blood stream and are excreted renally.

Unfortunately, the ASR also has a second major problem that may be common to all metal-on-metal implants with large diameter heads. The heads are creating too much stress in the area where they attach to the stems (the “taper junction”) and cause release of debris. It is likely that design modifications to stems over the past decade are responsible.

Oversight

Hip replacement or resurfacing are common procedures; however, the evidence highlights that regulators, industry, and the surgical community are not equipped to deal with and prevent further problems.

The European Commission’s solution is to oblige all EU countries to use a central European Data Bank for Medical Devices (Eudamed).²⁹ The aim is to strengthen surveillance of devices after approval (in current use) by providing

regulators with fast access to information. Yet the central repository is not publicly accessible, even to researchers, and the burden of responsibility for submitting data lies with relevant authorities in individual countries rather than manufacturers. Many problems exist with this approach, and there is uncertainty about whether it will improve safety.

Raised cobalt levels have been found in newborns of mothers with metal-on-metal hips

But a far bigger problem is the process for regulatory approval of new devices. Guidelines from the EU for manufacturers state: “The depth and extent of clinical evaluations should be flexible and not unduly burdensome.” This seems curious given the potential risks associated with some medical devices. Even more concerning, the current CE regulatory framework allows clinical evaluations of hip replacements to be based on existing technologies rather than the actual device and the clinical data submitted to be based on a literature review alone. Hip replacement systems were considered class II devices until February 2007, when they were reclassified as highest risk, class III (the same as other invasive devices such as defibrillators).³⁰ Class II devices have substantially lower evidence requirements that do not include an assessment of patient safety. Because of transition arrangements it was not until 2010 that all hip implants on the market had to meet the stricter standards.

Failings continue after approval. The MHRA received evidence that the ASR was a danger to health as early as 2008, yet it took two years before it issued a medical device alert (MDA/2010/033) requiring systems to be in place for the follow-up of patients with metal-on-metal hip replacements including, where appropriate, measuring blood metal ion concentrations and cross sectional imaging.³¹ The MHRA somewhat played down the problems, stating, “The majority of patients implanted with MoM hip replacements have well-functioning hips and are thought to be at a low risk of developing serious problems.” During this time the MHRA was using information from the National Joint Registry (NJR) for England and Wales, to inform its decision making.

The problem with using the NJR is that it records revisions. Thus the patient has to develop symptoms and present them to an orthopaedic surgeon, who has to investigate these symptoms and then consider revision. Only when that joint is removed will the information reach the registry offices. There is a further considerable time lag before data are analysed and finally presented. In fact, in some cases there is confusion about how “revision surgery” is defined.

Similar problems occur in the US, where most hip implants are evaluated through the FDA’s 510(k) programme, under which manufacturers have only to prove that they are “substantially similar” to other devices already on the market. As of 31 December 2010, the FDA had cleared for marketing 175 submissions for metal-on-metal hips through this route, including the the DePuy ASR implants. Several others are also now failing.

The Institute of Medicine has recently advised the FDA that the system for approving medical devices is not fit for purpose, recommending the elimination of the 510(k) process.³² In response, a US bill currently before the Senate would allow the FDA to compel manufacturers to track implant performance after approval and would also increase scrutiny on recalls. Yet at the same time, manufacturers are lobbying for a faster route to market.³³ The institute’s report concluded that “the FDA’s finite resources would be better invested in developing an integrated pre-market and post-market regulatory framework.”

No premarket system can ensure all devices are safe, but they can certainly make it more likely. At a minimum there should be an elimination of the use of multiple predicates in 510(k) and CE approval. Creating an independent system for post-marketing analysis for implantable medical devices that is robust and increasing international coordination around device alerts and withdrawals should go some way to sorting out the current mess.

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Competing interests: All authors have completed the ICJME unified disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work; CH has received payment from Channel 4 and the *BMJ* for publications related to medical devices and from BUPA for critical appraisal of guidelines on orthopaedic interventions. He has also received payment for workshops teaching evidence based medicine and expenses from the FDA to attend a device regulation workshop. MT has received payments for workshops teaching evidence based medicine and has received reimbursement for travel to attend the European Society for Paediatric Infectious Diseases and the American Association of Clinical Chemists. DJL has received payment for one educational lecture at a Finsbury conference in 2010 and has received travel and accommodation reimbursement from DePuy, Zimmer, Smith and Nephew, and Wright Medical to attend educational conferences. He worked as an unpaid consultant for Wright Medical in 2010 and is an expert witness in litigation against DePuy for the ASR implants.

Provenance and peer review: Commissioned; externally peer reviewed.

References are in the version on bmj.com.

Cite this as: *BMJ* 2012;344:e1349