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To The Clerk
Science and Technology Committee
House of Commons
7 Millbank
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Dear Clerk

Medical Implants: response to the Science and Technology Committee plan to examine the regulation of medical implants on behalf of the Centre for Evidence-Based Medicine and the BMJ

This response reflects the research and investigation studies that the British Medical Journal and the Centre for Evidence-Based Medicine have undertaken in this area. These include analyses of UK and US regulators as well as studies on metal-on-metal hip implants and research into medical device recalls and the device regulation process in the UK.

Our response to specific questions:

1. **Are current legislation and regulations on safety and efficacy of medical implants fit for purpose?**

Lack of pre market clinical data

Our research into European device directives that form the current legislation reveals the extent of the problem. First, it is left to the discretion of the Notified Bodies (as to the extent and nature of clinical data required for the approval of even the highest-risk devices). [1,2,3] We have found that whatever clinical data are reviewed by Notified Bodies, on behalf of the manufacturer, none are available to independent scientific scrutiny. This means that the normal level of evidence required to demonstrate the effectiveness or safety of new pharmaceutical agents is simply not required for medical devices under the current legislation. Given the large number and potential risk of medical devices, this lack of clinical data at the outset seems unacceptable, particularly for implantable devices (such as cardiac pace makers, artificial joint implants, stents etc.) which are those that present the highest risk.

The level of clinical data required for a new device can be minimal. For example, a directive would include as evidence for approval "a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device". This is a very low level of evidence and could be obtained in a few days, contrasting markedly with the type and extent of clinical trial data required for new drugs. [4]

The specific council directives [5, 6, 7] allow studies of other similar devices to be sufficient in a literature review for regulatory approval

►*B COUNCIL DIRECTIVE 93/42/EEC and 90/385/EEC*

- *(k) 'clinical data' means the safety and/or performance information that is generated from the use of a device.*

Clinical data are sourced from:

- *— clinical investigation(s) of the device concerned, or*
- *— clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated, or — published*

and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated.

Use of "equivalence" in regulatory approval of devices

A major problem with the current system is the use of "equivalence" (as outlined above) for approval of devices. That is, if a device is similar to another manufacturer's device on the market, then there is no need for clinical trials and device manufacturers can seek regulatory approval based on a far lower level of data than devices not considered under this fast track pathway. Regulators find it incredibly difficult to judge if a device is "equivalent" to another on the market. [9] As an example we have recently demonstrated for metal on metal large diameter hip replacement prostheses, that small changes to the design had sizable negative impact on the effectiveness and safety of the device. Rather than improving the device, the small change led to an unacceptably high failure rate with serious actual and potential impact on patients' health. However, in the US regulators suggested that: "*The design, while not identical to the predicates, does not raise any new issues of safety or effectiveness."* [9]

The current system of 'equivalence' and the acceptance of studies of other devices reported in the scientific literature are one of the main drivers of poor quality under-researched devices on the market today. Of more concern, the guidelines in the EU for manufacturer's state: "The depth and extent of clinical evaluations should be flexible and not unduly burdensome." The current CE regulatory framework allows clinical evaluations to be based on existing technologies rather than the actual performance of the new device.

Disparity in evidence requirements between US and EU

Similar concerns have recently been raised in the US, by the highly prestigious and independent Institute of Medicine about the FDA's fast track approval route known as 510k. Indeed legislation is currently before Congress to limit the use of this approval route by the FDA. [7] Their report on the 'Public Health Effectiveness of the FDA 510(k) Clearance Process' (http://www.iom.edu/Activities/PublicHealth/510KProcess.aspx) recommends:

'The Food and Drug Administration should obtain adequate information to inform the design of a new medical-device regulatory framework for Class II devices so that the current 510(k) process, in which the standard for clearance is substantial equivalence to previously cleared devices, can be replaced with an integrated premarket and postmarket regulatory framework that effectively provides a reasonable assurance of safety and effectiveness throughout the device life cycle.'

There are profound differences in evidence requirements for regulatory approval between the US and EU, with far higher requirements in the US for approval of the same device. For example, evidence submitted for EU approval of a "GuardWire" developed by PercuSurge for use during angioplasty, required a 22 patient study with no control group. In the US, in contrast, for the same device FDA regulators required an 800 patient multicentre randomized controlled trial. Although it is inevitable perhaps that different countries will have different processes and evidence requirements for medical devices, the magnitude of the disparity suggests an unacceptable level of risk for patients in the EU compared to the US. [10]

As a result a number of devices that were rejected by the FDA have been approved by the EU regulatory system. [3] This list of EU approved devices that were rejected by the FDA includes the PIP breast implant which has so spectacularly failed patients in the UK and Europe at enormous additional cost, and the now recalled metal on metal hip resurfacing prosthesis, the ASR, which resulted in joint failure and further risky and expensive surgery for large numbers of patients.

Rejected Devices by FDA that were approved in the EU:

Covidien PleuraSeal lung sealant system
This device went on the EU market in November 2007 and is used during elective pulmonary resection as an adjunct to standard closure techniques for visceral pleural air leaks. However, the Investigational Device Exemption (IDE) study (a clinical study for FDA regulatory purposes) produced unexpected interim results. In October 2010 Covidien announced a worldwide recall of all PleuraSeal lung sealant systems

Medtronic Chronicle
The Chronicle is an implanted system designed to measure and record haemodynamic variables continuously. In March 2007, an FDA panel refused to approve the device, citing statistically insignificant results as "lack of clinical effectiveness." It was nonetheless approved in Europe.

PIP breast implants
In 1991, breast implants manufactured by Poly Implant Prosthese (PIP) received a CE mark for its silicone breast implants But in 2001 they changed the gel, so that it was different from the one described in the CE marking file. This modification led to rupture rates higher than silicone implants made by other manufacturers. On 30 March 2010, the French regulator—AFSSAPS— issued a recall of all pre-filled silicone breast implants manufactured by PIP, affecting an estimated 35 000-45 000 women worldwide.

Trilucent breast implants
First marketed in the UK in 1995 by LipMatrix, Trilucent implants were recalled and withdrawn from the market in 1999. The filler of the implants, which was derived from soybean oil, broke down in the body and leaked through the shell, causing ruptures. The breakdown of the filler was significantly different from that predicted during preclinical testing, and many patients had to have implants removed.

Conor CoStar drug eluting stent
CoStar is a cobalt, chromium, paclitaxel eluting coronary stent and received EU approval in 2006. In May 2007, Johnson and Johnson announced that a pivotal clinical study of the device had failed to find a significant difference on the primary end point, possibly because patients got a suboptimal therapeutic dose of paclitaxel. The trial did not identify safety issues. As a result of this trial, Conor terminated ongoing clinical trials and chose not to conclude the submission of its US premarketing approval. Conor discontinued the sale of the stent in Europe, Asia, and Latin America.

Reproduced from Cohen D. Out of joint: the story of the ASR. BMJ. 2011 May 13;342:d2905. doi: 10.1136/bmj.d2905.

Changes to a device
In the US, even changes to the device which are regarded as minor - and which can be justified as not risking any material change to the risk-benefit equations for the patient - still need to be notified to the FDA 5 days beforehand. This is not the case in Europe. This is how the silicon in the PIP Breast implant could be changed without requiring notification, whereas in the US, any such change would require notification to the FDA approval. [11]

2. How effectively does the MHRA implement the Directive in the UK?

MHRA lacks access to clinical data submitted for device approval
The absurdity of the current system is highlighted by the minutes of a meeting of the MHRA's safety of devices committee in 2009 which stated: 'It was also noted that MHRA does not see the clinical data that is generated from a clinical trial prior to it being submitted to a Notified Body as part of a conformity assessment process. The only way they see it is if there is an adverse event or concerns raised. It is not mandatory for manufacturers to present their final report to the Competent Authority.' [9]

This leaves us in a situation where no one really knows, including the regulators, what data was submitted by whom, and on what date, for a device to be allowed access to the European market. Indeed, there is no complete list of medical implants that are on the market. It is difficult to understand how a regulator can function effectively without actually knowing what they have approved.

Unlike in Europe where both the public and, bizarrely, the regulator are kept in the dark, in the US, the FDA does itself see the data and provides public access to it on their website at the time of regulatory approval.

Slow responsiveness of MHRA

In addition to the lack of access to data prior to approval, we are also concerned about the slow response of the MHRA when safety or effectiveness concerns are raised on devices that are already approved or in use. For example, an unpublished trial of a metal-on-metal total hip replacement implant was stopped early due to problems with the device, but it took more than a year for the UK regulator to inform orthopaedic surgeons not to use the implant. Indeed, the MHRA confirmed that they did not know the trial was underway. [12]

The failure in some cases to evaluate rapidly devices in which concerns have been expressed seems quite unacceptable. Doctors have said that the MHRA is slow to respond when they do raise concerns.

Because of a lack of formalised post-marketing surveillance studies, the MHRA relies on either clinical registers to report failures (such as the national joint register) or issues being raised in the published literature. Both of these systems have their flaws —not least publication bias or under-reporting—and are not good for early warning systems or for spotting new conditions as they emerge. For example, joint registers only include patients who have had revision surgery, which may be many years after symptoms first occur. [13]

Lack of post market surveillance

We appreciate that a proportion of devices will fail owing to problems which were not noted prior to approval, in the same way that some medications need to be withdrawn from the market or their use restricted due to safety concerns. However, it is interesting that car manufacturers appear to be more successful at identifying and acting on possible faults in new cars than medical device manufacturers. This may be because there is currently no formal system for post market surveillance of medical devices in the UK and many vested interests that disincentivise manufacturers and clinicians from highlighting problems as they arise. Registries of devices are used in two main areas, orthopaedics and cardiovascular devices. However, these are ad-hoc and often not formalised. They may also not be totally independent of manufacturers and data can be difficult to access.

Unfortunately registries are limited to devices within these categories. And even in these limited clinical specialties, there is no way of knowing which patients in the UK have a device (even an implanted device), since this information is not available on GP records, and is not routinely noted on hospital records (or discharge summaries). Therefore, if a device is found to be faulty there is no way of notifying GPs or their patients.

This seems unacceptable given that the devices were purchased using NHS funds, and when devices fail the NHS is responsible for any costs incurred–unless there is ensuing litigation. A further consequence of this is that without systems to identify which devices are used in which patients, it is not possible to perform the large scale research on safety and effectiveness on medical devices using the many excellent sources of national data available to researchers in the UK (such as Hospital Episode Statistics, General Practice Research Database etc.). This contrasts with the situation for medications, where prescribing data are routinely available and widely used for studies in the UK. The addition of correct coding of devices in patient records would involve minimal cost, but potentially large benefit.

Lack of post market monitoring of performance
It is currently the case that CE marked devices can enter widespread use without any organised monitoring of the outcomes of their use. The MHRA itself has reported that "*Long term outcomes of implanted devices are a particular concern."* [14]
(http://www.mhra.gov.uk/home/groups/clin/documents/websiteresources/con082076.pdf)

The MHRA also reported to the BMJ that it relies on a "statutory vigilance or voluntary adverse incident reporting system" to regulate—in other words, governmental regulation really starts when devices are already on the market. [15, 16]

Under-performance of post-marketing surveillance by manufacturers
The extent to which manufacturers undertake post-marketing surveillance is currently unknown. Rather than have large post-marketing studies, manufacturers may rely simply on feedback from users. Steve Owen, head of Devices Policy, European and Regulatory Affairs at the MHRA, has stated that he finds it "staggering" how many manufacturers fail to fully fulfil their legal responsibility to collect product data once their device is on the market. [3]

And according to an MHRA report: "Post-market surveillance has not been addressed sufficiently in the past, as many manufacturers do not focus on this area, and it is not 'policed' vigorously enough by Notified Bodies." [3]

Manufacturers cannot be simply relied on to undertake post-marketing surveillance. Post-marketing studies, requested by the FDA for breast implants in 2006, have lost so many of the women they were supposed to follow up that they are unlikely to offer any insight into the long term safety of devices. After three years, a study by Mentor, the maker of Memory Gel implants, lost 79% of the patients enrolled, whereas Allergan, the maker of Natrelle implants, has lost nearly 40% of its participants after two years. [10]

3. How could the legislation and regulations be improved?

Independent scrutiny of premarket approval data
There appears to be a concerning lack of transparency in the data available for independent scrutiny of medical devices. We recently quantified the number and types of medical device failures in the UK, the health consequences from these failures, and the data that had been supplied for premarket approval. These appeared to be straightforward questions—ones that someone else would have already asked—but unfortunately our research threw up numerous hurdles. Indeed, we were not able to gain access to any data submitted by device manufacturers for regulatory approval, and thus were not able to judge whether device failures could have been predicted by lack of clinical data prior to approval. [8]

In the absence of publicly available regulatory data, it is left to the device manufacturers to decide what enters the public domain on their website or as a scientific publication. This means that clinicians are dependent on the manufacturers to provide them with data about their implant and what they decide to publish. As noted above, this lack of independent assessment of data is not acceptable, and contrasts with the UK's highly regarded systems for evaluating clinical evidence via NICE etc. [4]

Lack of clinical trial data and cost effectiveness

The lack of data does not help clinical decision making. Indeed, the lack of clinical studies or trials makes it an almost impossible task for health technology appraisal. With drugs, the likes of NICE are able to use the data generated in regulatory approval to make decisions about the best use of NHS funds. We have been told by similar institutions across Europe about the impossible task in trying to prioritise healthcare spending for devices. In the worst case scenarios, patients may be subject to an intervention that is not appropriate for them. In addition the lack of clinical data means it is difficult if not impossible for commissioners of health care to understand the true cost of interventions beyond the initial cost impact analysis. [8]

We urge the Committee to push for increasing the access to pre-market approval clinical data used by Notified Bodies to submit for regulatory approval.

Failures to identify and recall devices when concerns are raised

A second problem highlighted by our research is that information about the number of recalled devices, the risk of harms to patients, and the premarket approval process was not available from the MHRA. [8] These data are held by the manufacturer and the Notified Body. Since both the Notified Bodies and the manufacturers are exempt from freedom of information legislation, we decided to contact them directly by email. We started with the manufacturers of 192 devices recalled by the MHRA over a 5 year period, each of which lists a contact responsible for the recall. Unfortunately, despite our best efforts (based on high level clinical research expertise) only four (2%) companies provided any clinical data. We were informed by the Notified Bodies that information was confidential and not available for scrutiny. [3, 4, 8]

In addition, our attempts to obtain how many adverse events had occurred for specific devices were also unsuccessful. [8] The Freedom of Information Act is over-ridden by medical device legislation in the EU. Article 20 of the EU medical devices directive states: “Member States shall ensure that all the parties involved in the application of this Directive are bound to observe confidentiality with regard to all information obtained in carrying out their tasks.”

Therefore we urge the Committee to strengthen the Notified Body assessment in terms of demonstration of competence, impartiality and transparency, providing for timely and uniform action in the areas of vigilance and reinforced market surveillance. In addition we add the need to allow independent third party scientific scrutiny of data supplied.

Post marketing surveillance

At a minimum there is a need to eliminate the use of multiple predicates (equivalence) in 510(k) and CE approval and put in place robust post marketing studies to detect devices that are failing.

Funding medical device safety with an insurance based system

No initial regulatory evidence can safely assume that there will not be harms in the long term, so devices could come with an insurance based funding system to allow for this—companies go bankrupt and harms take a long time to manifest. In effect the greater evidence of safety would lead to reduce premiums at the time of implantation. [11]

Transparent approach to conflicts of interest

It is important regulators remain impartial and take a view point that is important, not only for industry, but also for patient safety. The use of impartial advice is paramount in regulatory decision making processes where substantial sums of money are at stake. To achieve this, the regulator and the regulations need to have a consistent and transparent approach to dealing with conflicts of interests.

4. **How could the European Commission ensure that potential changes to the Medical Devices Directive do not hinder the introduction of innovations in medical implants to the market?**

Failures of medical devices cause harm and cost money. More stringent requirements to provide evidence from clinical trials for the efficacy and safety medical devices before they are approved should therefore be welcomed by patients, clinicians and the medical device industry. Devices which are safe and effective provide a win-win situation where both the company gains market shares, and NHS patients benefit from improved clinical outcomes. Innovation is only of real value to health if it does genuinely improve outcomes–unfettered innovation may have the opposite effect.

Different levels of evidence

The European Commission should consider different levels of evidence depending on what is currently available. Where multiple devices for the same condition currently exist (e.g., hip replacements, pacemakers), then the bar for seeking market entry should be higher. Where in contrast little or no devices are currently available and patient care is clearly suboptimal, then consideration can be given for earlier or faster approval of innovative devices which are clearly filling clinical gaps. This parallels the lessons from the pharmaceutical industry, where for example HIV drugs underwent fast track approval in their early years due to overwhelming patient need, but now with many combinations of HIV drugs now available a higher level of scrutiny is now needed.

We believe that there is a need for a clearer understanding of evidence requirements for new devices.

Better methods for surgical innovation: the IDEAL framework

The IDEAL (Idea-Development-Exploration-Assessment-Long term study) framework and proposals are being developed by an international group of methodologists and clinicians. [17-19]
IDEAL promotes: the development of innovative study designs for early phase innovation in interventional therapy in surgery, including the development of implantable devices, and a comprehensive international agreement on best practice in conducting and reporting clinical case series in surgery. The IDEAL group also recommends that regulators of medical devices provide rapid, flexible, and expert ethical oversight for early-stage innovation, link provisional approval to evaluation or registration of all cases and raise the burden of proof for full licensing of new devices to demonstration of efficacy level.

Much has been made of the difference between medicines and implantable devices. [20] However, it is worth noting that if an implantable device is faulty or fails, the reversal procedure carries risks in itself. There are the risks of having to undergo an anaesthetic plus there may be other risks from the procedure itself, for example haemorrhage, infection and venous thromboembolism. The current system should strive to incentivise innovations that improve patient care and reduce the harms to patients.

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