PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	**Medical Device recalls in the UK and the device regulation process**
AUTHORS	**Heneghan C, Thompson M, Billingsley M, Cohen D**

VERSION 1 – REVIEW

This paper was previously submitted to the BMJ and peer reviewed by Prof Steven E. Nissen, Cleveland Clinic, USA and Prof Nick Freemantle, Professor of Clinical Epidemiology & Biostatistics, Department of Primary Care and Population Health, University College London, UK. The authors' responses to the reviewers, BMJ editors and editorial committee are included below.

VERSION 1 – AUTHOR RESPONSE

1) We were pleased with the Peer Review comments from international experts in this field, which highlight the importance of the work:

For instance this is what Reviewer 1, Prof Nissen states:

'I enjoyed reading this manuscript. Interestingly, the weaknesses of the manuscript (inadequate sources of data) actually represent a strength of the study.

The authors reveal critical flaws in the approval process for medical devices in the UK and demonstrate an extraordinary lack of transparency in both the approval process and procedures used for withdrawal of devices with safety problems. The inability of the authors to access reliable data on medical devices represents the most important finding.'

Of interest is that Nissen's viewpoint is in fact mirrored by that of the Medicines and Healthcare products Regulatory Agency (MHRA) itself, who also have some concerns about the current system, noting "*the evidence on safety and efficacy of new devices and new procedures at the time they are introduced into UK practice is very variable*." [1]

Reviewer 2, Nick Freemantle, states

'*Thank you for sending me this interesting paper for comment. I have a couple of suggestions which I hope will prove helpful. Overall this is a well written and interesting paper which I believe will be of interest to readers of the BMJ and will highlight limitations in the manner in which devices are currently being regulated in Europe*.'

We feel the Reviewers' comments support the argument that the paper presents research findings that are of significant public health interest. Our findings are in accordance with a similar piece published in Archives of Internal Medicine [Zuckerman] that looked at recalls of medical devices in the US. That article demonstrated "systematic problems" in current medical device regulation "that have exposed patients to serious harm," Our manuscript provides the first description of the potential

magnitude of problems with device regulation in the UK and EU market as a whole, and thus provides new information.

2) The manuscript Committee noted: 'the explanation of the approval and notification processes in the various countries was hard to understand. We wondered if a graphic of some sort might make things clearer.'

We agree the process of regulation of medical devices is difficult to understand. We ourselves had difficulties the first time we interpreted the process, given the myriad of organizations involved and the somewhat opaque processes. For many general medical readers this may be the first time they have read about the details about how devices are regulated. Indeed, not all manufacturers are aware of their responsibilities and not all purchasers are aware of the true meaning of the CE mark. [2] Adding a graphic to provide a clear visual description of this process is an excellent suggestion. For better understanding we have decided to position such a graphic in the associated commentary in the BMJ. In addition, the related analysis piece in the BMJ to the paper will explain further some of the intricacies and difficulties in interpreting the regulation.

3) The Editors were also concerned that:
The level of agreement between the two reviewers was not particularly high and although disagreements were resolved it isn't clear how that happened and whether it might reflect dominance of one reviewer. It would be ideal to present the figures for each reviewer.

We weren't clear on what standards were used to make the judgments about likelihood of harm. It seems this is quite a subjective decision. We were concerned that a) the two reviewers, who are authors and presumably have a point of view about the matter, are not impartial and b) are not subject matter experts -- we think very specialized knowledge might be needed to assess the possibility of harm.

Reviewer 2 also stated
I am not sure that the kappa statistic is particularly informative here; and dichotomising a kappa of .6 as moderate and .66 as good association, makes quite a big jump in interpretation for a little difference. Given the importance of the classification the authors might want to provide the relevant contingency tables for overall and class III device classification (that were used to calculate the kappa score) in order that people may make their own judgement on the validity of the categorisation.

Reviewer 2 also recognizes that:

'In general the paper is well written and the methods are clear, at least to this reader who has conducted a number of randomised studies of devices and been involved in regulatory work as part of a PMA application to FDA based on one of his trials.'

Our review methods were much more substantive that the recent paper by Zuckerman published in the Arch Int Med. [3] In that article the authors did not report agreement at all and provide substantially less detail on their methods. However, the Committee was correct, our decisions were subjective. As in any systematic review of literature or data, we set out a priori the criteria used to assign categories to each piece of data (in this case the safety alerts), in the same way that we would use for systematic reviews (inclusion/exclusion criteria, risk of bias, data extraction etc). However, given the subjective nature of such decisions, we felt that there was a need to assess agreement. Importantly, our approach was systematic, thus it could be reproduced by other researchers, who might as the

In terms of subject experts both authors who undertook the assessment are General Practitioners. In our practice we manage and care for patients who use this wide range of devices (from contact lenses, and wheelchairs, to implantable cardiac devices). We are not aware of any particular expert who could provide a more general assessment of the potential for harm from this range of defective devices. What is important is that our methods were explicit and can be reproduced by others.

In respect of the agreement we have added a contingency table as asked for by one of the reviewers:

Reviewer ratings of Medical Device Alerts FDA recall status

Reviewer	FDA recall Class I	FDA recall Class II	FDA recall Class III	Uncertain
Reviewer 1	177 (39.6)	205 (45.9)	32 (7.2)	33 (7.4)
Reviewer 2	189 (42.3)	169 (37.8)	66 (14.8)	23 (5.1)
Agreed total*	197 (44.1)	168 (37.6)	54 (12.1)	28 (6.3)

Kappa for overall agreement 0.6

We have removed the kappa for class 3 device as requested by the reviewer and now describe the overall agreement as moderate and discuss the implication of this further in the discussion

We have also added to the limitations in the discussion particularly emphasizing the limitations of our own judgements and the fact we are unable to fully assess the true number of patients harms:

Limitations:

The main limitation of the study was the lack of available data on details of device withdrawals, or quantification of the number or current use of devices affected. Our CE classification of devices and FDA recall status was therefore based predominantly on our clinical experience based on the information that was publically available, and this judgment may therefore differ from manufacturers' classification and form other clinicians. Owing to a lack of data made available to us, we were also unable to determine the reason for the rise in Field Safety Notices, and therefore cannot speculate on when the problem first arose, and more importantly, what kind of clinical testing had been undertaken prior to the device going on the market. The absence of a central registry containing information on how many devices are currently in use in the UK limited our ability to fully assess the implications of our findings on patient safety. This means we are unable to quantify the true number of patient harms caused by medical device recalls Finally, we are unable to determine which of the safety alerts were acted on by the health care and social care community, the proportion of patients (and/or devices) who needed to be traced, and the workload and costs involved in these actions.

4) The Committee queried:

We wondered if the fact that the number of alerts has increased might be a good rather than a bad thing and reflect higher standards for devices and a lower threshold for identifying and acting on problems. We thought it was difficult to evaluate this number without knowing the denominator, in other words the number of devices in the market in each year.

This is a fair point and we make reference to this exact point in our discussion.

Page 7 of the manuscript: Implications: *One reason is medical device numbers have increased substantially over time. One could also argue manufacturers are doing their job, the question then is how many device alerts could or should there be?*

In asking for the denominator data, the Committee ask for data that is currently not possible to know. Unfortunately, the MHRA does not hold a central registry of even the highest risk implantable Class III devices. However, there are estimated to be between 80,000 to over 200,000 devices in use in the UK. Given the findings of a systematic review of adverse drug reactions which found the median under-reporting rate for drugs across 37 studies was 94% (interquartile range 82–98) for adverse reactions, the true figure for devices may well be similar. Even at the lowest estimate, the device recalls still represents a substantial impact on patient care and NHS workload [ref 4, 5, 6]

5) The Committee were concerned that the paper did not seem to really "quantify" harm in the way the title suggested it would; ordinarily we would expect to see some evidence of real harm rather than speculation.

Our findings are in accordance with the recent paper in the US by Zuckerman in Archives [3] which concludes 'that reform of the regulatory process is needed to ensure the safety of medical devices.' Our initial aim was to quantify the amount of harm caused to patients by medical devices (e.g. device specific morbidity and mortality). However, this level of data is simply not available under the current system. Although this is disappointing, in fact as the reviewers also note, this is an important take home message from the paper. The lack of transparent data on medical device associated harms is surely of interest to the general reader, and the public at large. We agree that it would be reasonable to reword the title to a much simpler format. We'd be happy to take Editorial advice on this.

Because we were unable to actually quantify the consequence we have changed the title to

Medical Device recalls in the UK and the device regulation process

6) We felt uncomfortable about the assertion of a lack of responsiveness from the companies that were contacted. The process by which these companies were contacted was not well described. In similar papers it is usual to present a flowchart of how people were identified to contact, details about how they obtained information, contact attempts and methods, success at each point and so on.

We are unsure where similar papers exist as to our knowledge this is the first ever paper to report these findings in the UK. It would be helpful to clarity the similar papers referred to. In similar systematic reviews of interventions for example, authors often state that "authors and content experts were contacted" yet there is no format for describing further details of this. In the methods section we note that we wrote using an email address to the person or organization noted in the safety alert as the person nominated (by the manufacturer) as responsible for handling queries for this device. This seems an absolutely transparent and logical approach to take. We would be happy to supply this information and we have added the content of our emails as an appendix to the manuscript, again providing opportunity for other researchers to repeat this if necessary.

We have attached the list of questions asked to the manufactures and the notifying bodies as appendices

The process of emails is also described extensively in the accompanying commentary and analysis piece in the BMJ

7) Reviewer 1 I think the authors should consider adopting a more scientifically "neutral" tone. The findings are shocking enough without any further emphasis on the incredible inadequacy of the current system.

We have undertaken this relevant point and adopted a more neutral tone.

Specifically we have removed the following from the discussion:

Classification systems are important as they underpin the clinical data that should be required prior to approval, with presumably higher standard of clinical data required on devices associated with higher clinical risk. Yet these requirements are evaluated by Notified Bodies who tend to function in a closed manner that provides little visibility on either the criteria required for approval, or clinical data supplied prior to approval. 16 In addition, the single market approach for devices means certification is performed only once for the whole of European market.

The device industry appears to have successfully persuaded regulators that the evidence from randomised trials required for drugs is not necessary, 17 9 In the most risky devices, where trials exist, the majority are nonrandomized, single arm studies involving less than 100 patients.18 Even in the US, where FDA regulation is more stringent, pre-market approval of cardiovascular devices is often based on studies that lack adequate strength and are prone to bias.19

The fact that most clinical studies of medical devices are underpowered to detect unusual but potentially life threatening events, 9 underscores the need for post-marketing surveillance to identify subsequent device failures. Our study clearly highlights the absence of such transparent data, even for legitimate research groups.

8) I strongly urge the editors to commission a companion editorial that helps interpret the study's findings and make recommendations for urgent corrective action. Keep the article as scientific as possible, but include a strong commentary.

This has been done and will be published in the BMJ

9) However the paragraphs on device classification beginning 'Neither the Field Safety Notices nor the Medical Device Alerts…' is completely incomprehensible to me and could do with some careful attention as it is pretty key to the arguments being made.

We have rewritten this paragraph to improve the clarity and understanding

Page 4 paragraph 3 of the methods

10) The paper notes an increase in field safety alerts over time in UK. Given other countries (including those with different regulatory settings) have access to very similar devices, would it be possible for the authors to say something about the rate of recalls and regulatory notices in different jurisdictions? If FDA alerts have increased during this time then it would add evidence to the concerns raised in the paper about the CE marking process.

For this reader the paper could make some clearer comments about what needs to be done. First, is regulation of devices (particularly class III devices) adequate in Europe? If not, is there a better model (personally I believe that FDA is considerably more thorough, and with a much stronger link between evidence and marketing claims permissible, but it is not clear from the paper that the authors concur with this view.

Second, what safety data should be available for public scrutiny? This is quite a difficult area in pharmaceuticals where regulatory agencies would normally conduct appraisals in camera to avoid unnecessary concern and the risk of patients stopping drugs inappropriately. The airline regulators also work primarily in camera, only going public as final warnings against wrongdoing (for example on the Air Malaysia second occurrence of landing at LHR with insufficient fuel in the tanks – a private warning happened first time and a third occurrence would have led to a ban).

Third, can class III devices and pharmaceuticals be treated in a similar manner? I actually believe that they can, and the principals of safety efficacy and quality (of manufacture) fit very nicely with class III devices.

All of these are useful points. We are minded to tone down the research piece and therefore we are not addressing these points in the research manuscript but they will appear in the accompanying commentary and analysis piece in the BMJ

Yours Sincerely

Dr Carl Heneghan and Dr Matthew Thompson

References

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VERSION 2 - REVIEW

REVIEWER	***Steven E. Nissen***
REVIEW RETURNED	03-May-2011

GENERAL COMMENTS	This is a challenging manuscript to review because the principal finding is an extraordinary absence of reliable information on device approvals and withdrawals in the UK (and EU). Although the data

	are "lean", I strongly support publication as a means to focus scientific and public attention on the lack of transparency in medical device regulation. The manuscript is well written and the critical issues are framed appropriately in the discussion.

REVIEWER	***Nick Freemantle***
REVIEW RETURNED	03-May-2011

GENERAL COMMENTS	The authors have adequately addressed the concerns that I raised on a previous version of this paper submitted to BMJ