30-Nov-2015

Dear Mr. Marcus

Manuscript ID BMJ.2015.029502 entitled "REGULATORY APPROVAL OF INNOVATIVE MEDICAL DEVICES: A CROSS SECTIONAL STUDY"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Anita Jain
Editor The BMJ
ajain@bmj.com

https://mc.manuscriptcentral.com/bmj?URL_MASK=f3162c8d18b74f61b99be2fc0cba6923

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Jose Merino (chair), Doug Altman (statistician), Helen MacDonald, Georg Roeggla, Anita Jain, Rubin Minhas, Alison Tonks, Sam Parker

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

1. The abstract needs to be mde clearer. There is no explanation on the range and types of devices considered. The innovation may be minor in terms of clinical practice or may be a major advance.

2. It is likely that industry had very different publication practices about which studies to publish. There could be other reasons for the publication gap seen which need to be discussed.

3. The paper seems to reflect not the first-in-man study but first published study.

4. It might have been preferable to start with regulatory applications then go back and look for studies to support the approved devices, or compare the evidence on approved v/s not approved devices. The context and relevance of choosing to start from publication needs to explained.

5. The actual issue needs to be made clearer: High risk devices? Rapid approval? Approval in the absence of evidence?

6. Can devices be approved without a "first in human" study? If so, they aren't captured here. The authors should define a "first in human" study.

7. Based on the short approval time it would be worth expanding the study to see how things have altered over time. And particularly in the last 3 years.

8. This statement is not clear: "We included articles that reported a first-in-human study of an innovative medical device. We excluded articles if they only reported a preclinical study of a device because very few such devices are ultimately translated.[11]"

9. You may look at recent BMJ Analysis on regulation of devices. There are distinctions drawn in device rules such as the difference between humanitarian devices for rare diseases and high risk implantable devices versus monitors etc. These are not mentioned.

10. Please explain 510K pathway and other mechanisms for device approval (perhaps in a box)

11. International relevance is lacking as regulatory approval differs across countries. Please provide the context for regulatory approval of devices in other countries, and how these findings may/ may not be relevant.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors,

explaining how you have dealt with them in the paper including a marked copy of revisions made.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
Comments from Joseph P. Drozda, Jr., M.D.

This is an observational study of innovative medical devices with first-in-human studies published in 2000-2004 that were subsequently approved by the U.S. FDA. The authors found that just less than half of devices received regulatory approval, that the 510(k) pathway was the most common route to approval, and that industry collaboration was associated with significantly greater success in achieving FDA approval. These authors previously published a study of the translation of innovative devices from the laboratory to first-in-human studies.
In general, this is a methodologically sound study that was likely to capture most studies of novel devices that were published during the specified time period. It explores further a matter of increasing policy interest, i.e., the processes by which medical devices are developed, approved, disseminated, evaluated with respect to real world effectiveness, and iterated to improve performance or removed from the market for lack of effectiveness or safety issues. An understanding of these processes is important in an era of health care delivery and payment reform because of the simultaneously increasing utility and costs of medical devices. The FDA is currently evaluating this medical device ecosystem with respect to both premarket approval and postmarket surveillance. Most clinicians are unaware of the details of the medical device approval process and would benefit from the information presented in this study. For instance, it appears odd that the most common pathway for regulatory approval of innovative devices is the 510(k) process, which is designed for devices that are substantially similar to existing devices.
I have the following specific comments:
• The following sentence appears in the abstract (lines 56-7): "The proportion of devices receiving regulatory approval was then compared using the Chi-square test." This leaves the reader wondering, "Compared to what?" The question is answered in the Methods section of the paper (lines 164-171). I know that this paragraph cannot be reproduced in the abstract but a brief statement regarding the comparison should be included.
• An important part of this study as stated in the Introduction was the assessment of the roles of academia and industry in obtaining regulatory approval. According to the Methods section (lines118-120), the involvement of industry was determined in the papers describing the first-in-human study. I would think a better source of that information would be the FDA regulatory documents since it is possible that industry could have become involved with a device after the first-in-human study or could have abandoned the product before regulatory approval (less likely).
• The most significant concern from a methodological perspective is the process by which studies were selected for analysis. This process winnowed the 5,574 papers identified in the PubMed screen down to 218 included studies and involved significant judgment at each step, e.g., 5,081 records excluded based on titles and abstracts. The methods used for making these judgments should be clarified. For example, were all abstracts reviewed and scored independently by 2 or more investigators? If so, what was the process for adjudicating differences in scoring?
• The first heading in the Discussion section contains a spelling error. It should read "Principal findings."
• The conclusions appear appropriate with the most significant and most concerning one being the large proportion of innovative medical devices being approved through the 510k process without rigorous clinical trial data on safety and effectiveness.

Additional Questions:
Please enter your name: Joseph P. Drozda, Jr., M.D.

Job Title: Director of Outcomes Research

Institution: Mercy Health

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may
in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way
gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: I was principal investigator of a collborative agreement with the U.S. FDA whereby Mercy integrated unique device identifiers into our electronic informaiton systems and created a database for postmarket medical device surveillance and research. (Contract number DHHS/FDA-22320172C from the Center for Devices and Radiological Health, USA Food and Drug Administration.) I have just been awarded a collaborative agreement by FDA for extending this work to 2 other health

systems. (FDA Grant Number: 1U01FD005476-01.)

Reviewer: 2

Recommendation:

Comments:
This study of device innovation has an interesting design and two main conclusions -- first that about half of published 'first in human' devices end up ultimately reaching the market and second that it seems that industry-originated devices have a better record of translation.

The first conclusion seems solid, and it includes the very interesting nugget that some of these reached the market before publication of the first human studies. This conclusion is limited by the small number of devices studied, relating to publications from over a decade ago. The authors justify this based on the time it takes to commercialize a product, but this is undercut by the authors' recognition that many devices are not studied extensively and their own conclusion that many of these devices are marketed before the publication of a first in human study. It's also worth considering the wide variation in device types that the authors evaluate, and whether it is fair to analyze an 'instrument' lumped together with an 'imaging' device. On the other hand, if the authors get too granular, then their relatively small N may lead to difficulties in making even qualitative comparisons.

I had more trouble with the second conclusion because I wondered whether it was more likely that an industry actor, driven by a profit-seeking motive, would publish an article about a successful device, and would not invest the time and energy in publishing an article about an unsuccessful device. By contrast, an academic investigator may be driven by norms to publish more extensively. I was therefore skeptical about the apparently significant comparisons the authors made. I'm not sure how to account for such potential bias in the analytic approach.

Specific comments:
-- I was confused a bit in the intro paragraphs, as the authors tried to contrast drugs and devices. Initially it seemed like there was a contrast between drugs and devices, but then in paragraph 3, the authors appear to claim that there are reasonable similarities.
-- Line 91 wouldn't say "report on"
-- Methods: Are kappa scores available?
-- Discussion: The FDA does not consider devices that reach the market through the 510K process to be 'approved.' The correct regulatory terminology in those cases is 'cleared.'
-- When is introduction of a product "regulated, structured, and not variable"? There's regulation around its approval/clearance process, but after that point the FDA's regulatory authority recedes.
-- Later in the discussion you should be careful about overstating the differences between drugs and devices; high risk devices at least are supposed to be tested in human clinical trials before approval.
-- A comprehensive online supplement of device names and studies would be useful.

Additional Questions:
Please enter your name: Aaron Kesselheim

Job Title: Associate Professor of Medicine

Institution: Brigham and Women's Hospital/Harvard Medical School

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may
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If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 3

Recommendation:

Comments:
the authors have done tremendous amount of work reviewing hundreds of papers and search seems to fit the purpose. They propose interesting strategy for future innovation in medical device area.
However, the idea of academia + industry partnership is not new and the industry is recently outsourcing the early

stage of innovation to academia. i have a few questions for authors:
1. for devices that were developed by academia alone was there an attempt to partner with industry? how do we know that industry didn't reject partnership based on their business calculations/considerations? so the main question is-- is the current low success rate possible change or reflection of industry profit consideration?
2. what do you think about higher rate of success when Industry did not work with academia? they certainly had higher success rate in terms of regulatory approval.. are these more likely to be breakthrough technologies where academia could help ensure better evidence generation? almost all PMA devices were developed by industry alone.. one might conclude that industry does not need the so called 'inefficiency' of academia when they develop ideas in house. Do you agree with this? if not, what can we recommendation based on your data to ensure that these technologies will be safe?
3. you have mentioned MDIC- it is a good concept. based on their work streams do you think it will create true partnership with academia to promote IDEAL guided evidence based innovation?
4. we see more and more devices fail recently because of 510K and even PMA not being adequate in ensuring safety in real work settings. success rate for approval is only business side of the coin and i believe that there is a need for public health side: ensure partnership of industry and academia for post-market surveillance. MDEpiNet is the organization that promotes this partnership. Is there any information about post-approval studies or research for these devices and how often industry and academia partnered not only for innovation but also for evaluation?

minor issues:
conclusions in the abstract states: 'We identified a multitude of innovative medical devices in first-in-human studies, almost half of which received regulatory approval'. one can conclude that only half of 'innovative' devices were ultimately approved-- were those NOT approved really innovative?
conclusion in the main paper: its too long, there should be no citations and discussion around drugs is confusing.

Additional Questions:
Please enter your name: art sedrakyan

Job Title: Professor of Healthcare Policy and Research

Institution: Weill Cornell Medical College

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?:

Funds for a member of staff?: No

Fees for consulting?: No

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Do you hold any stocks or shares in an organisation that may in any way
gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: none

Reviewer: 4

Recommendation:

Comments:
This paper considers an area which is under-researched. The title is misleading as only FDA approvals are studied. it is noted that this is because the USA represents the largest global market for medical devices but, inevitably such a strategy excludes any reference to the substantial EU system for approvals.
The methodology and search strategies are sound, however, it is unclear whether the pathway through concept, approval, clinical trial etc are common to the devices identified. Clinical trials may be rather different entities in the USA and the UK/EU, and may be very small in a local and limited population or fully powered. Whilst of interest, the data leaves many unanswered questions. it is acknowledged that these are difficult and may be impossible to answer but the potential 'disconnects' and limitations should be acknowledged.
The results are interesting however they represent a somewhat historical 'snapshot' and, although reference is made to the pathway for development, it is impossible for the reader to discern how many devices may have been conceived in an academic environment and then further developed through spin-out companies. To the best of my knowledge it is very unusual for development beyond initial concept and laboratory based proof of concept to remain in an academic setting, although some devices in very specialised areas for individual patients may do so. Despite the word limit, a little more context would be helpful otherwise it is easy to overstate the success of industry-led development.
My main concern relates to the diversity of devices and this is not captured. Numerically many industry devices are targeted to low risk applications, wound dressings being a common example. First in human studies carry low risk and there could be enough of these to skew the data. I note the distribution especially of instruments and implants but there remain many 'others'. The classification of devices according to the EU directive is not mentioned and the appropriate pathway for development of an active implantable device, a more traditional implantable that modifies

existing technology in a predictable way and that for a surgical instrument are very different which in turn impacts directly on whether 510(k) is a suitable pathway for approval in the context of first in human studies. It would be informative to either stratify the devices by classification or to limit those included to the higher risk and higher impact categories so 'apples and pears' are not being compared.
The IDEAL pathway is mentioned and the value of this initiative is acknowledged, however, this is of relatively recent origin and would not have impinged on the studies in the timeframe considered in the paper. Rather IDEAL is likely to guide and facilitate device studies conducted within the NIHR portfolio of research and under the auspices of HRARES. How this relates directly to the matter of FDA regulatory approval is not clarified. This comes across as an endorsement of IDEAL rather than directly informative to the main message of the paper. The main message is somewhat obscured by inclusion of IDEAL.

Additional Questions:
Please enter your name: Sheila Fisher (Dr)

Job Title: Hon Clinical Research Fellow (retired surgeon & former Chair MHRA Committee on Safety of Devices)

Institution: University of Leeds

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way
gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: I am a former Chair (2012-2015) if the MHRA Committee on Safety of Devices.
I currently Chair (2014 to date, have been a Member since 2007) a Health Research Authority REC flagged for devices, mental capacity act, paediatrics as well as CTIMPs, in which role we see a number of higher risk, higher impact and first in human device studies.

Information for submitting a revision

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2. Name of the ethics committee or IRB, ID# of the approval, and a statement that participants gave informed consent before taking part. If ethics committee approval was not required, please state so clearly and explain the reasons why (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines.)

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a. Title: this should include the study design eg "systematic review and meta-analysis."

b. Abstract: Please include a structured abstract with key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research). For every clinical trial - and for any other registered study- the last line of the abstract must list the study registration number and the name of the register.

c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

d. Methods: For an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found.

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i. For a clinical trial: Absolute event rates among experimental and control groups; RRR (relative risk reduction); NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000.)
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g. Footnotes and statements

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END

Date Sent: 30-Nov-2015