BMJ - Decision on Manuscript ID BMJ.2015.029502.R1

Body: 29-Mar-2016

Dear Mr. Marcus

Manuscript ID BMJ.2015.029502.R1 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 internally. 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 editorial review, 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. I am afraid we cannot guarantee publication at this stage.

Yours sincerely,

Anita Jain
Editor The BMJ
ajain@bmj.com

https://mc.manuscriptcentral.com/bmj?URL_MASK=1b566b28862c466c8e5fa481b8a1e31c

Report from The BMJ's editorial review

Decision: Put points

Detailed comments:

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 from the editorial review:

- Can 'innovative' be replaced with 'new' medical devices or just leave it at medical devices? At certain points, innovative is equated to novel (no previous clinical study) which may be misleading.

- Please clarify throughout the paper that 510K is a 'clearance' and not approval.

- Please elaborate why clearance through 510K pathway is a problem. It could be that this was a minor modification and did not require a clinical study as per FDA norms. We don't really know how incremental a device may have been and if 510K approval is indeed appropriate in those instances. Do you advocate changing that?

- You started with clinical studies to identify devices that did not receive approval. Might we have more details of non-approved devices?

- Also, for instance, in the supplementary table listing devices that received regulatory approval, might you instead list all studies/devices included and add a column of whether regulatory approval was received or not?

- It is not clear how you identify some devices cleared through 510K that did not have a prior published clinical study. If you start from clinical studies, how did you identify the reverse, i.e. approved devices with no prior published clinical study?

- What is the time period over which you searched FDA databases? Is it even before 2000 and so you identified 'cleared' devices and a clinical study that followed it?

- Is the comparison to drugs approval necessary? We wonder if it may be removed throughout.

- Reviewer comment: The conclusions are still overstating the importance of working with industry. Industry picks and chooses when to collaborate and they get involved when there is a greater potential for commercialization or when they know they will be successful. This is a serious bias that can't be adjusted for. The conclusions are still not impartial. I think the conclusions need to reflect the limitation of the data not just put in limitations that few people read.

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 and provide a revised document with track change as well.

** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:
The authors have satisfactorily addressed all of my comments and the revised manuscript is significantly improved.

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 collaborative agreement with the U.S. FDA whereby Mercy integrated unique device identifiers into our electronic information 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 am principal investigator of the BUILD initiative, which has been funded under another collaborative agreement with FDA and will extend this work to 2 other health systems. (FDA Grant Number: 1U01FD005476-01.)

Reviewer: 2

Recommendation:

Comments:
This paper provides a descriptive analysis of the early clinical testing reported in the literature for novel medical devices. This is an interesting and well-designed study, although the authors could better showcase the findings of greatest clinical and policy import and better contextualize these findings. Below are a few major and specific comments that the authors could consider in revising their manuscript.

MAJOR COMMENTS

1. The authors report that the (limited) clinical testing reported in the literature is often not accessible before new devices are cleared or approved by the US FDA. This is a novel finding that merits more attention in the text and that extends the work by Zuckerman et al. (JAMA Intern Med 2014;174:1781), which found that scientific data to support 510(k) device clearances is frequently unavailable in the mandatory FDA summaries, and Chang et al. (BMJ 2015;350:h2613), which found that the key study results for many of the highest-risk cardiovascular devices remain unpublished post-approval.

2. The finding mentioned in point 1 would be made stronger if the authors could characterize the type of studies they identified for each of the approved devices. How many patients did these studies enroll on average? What was the study design (randomization, masking, controls)? Were larger, higher-quality studies conducted after approval, or were the initial studies the best that clinicians got? This would provide some sense for the quality of the evidence available when these devices enter the market. Some relevant cites: Dhruva et al. (JAMA 2009;302:2679); Hwang et al. (BMJ 2014;348:g217); Rathi et al. (JAMA

2015;314:604)

3. The number of studies collected for PMA devices (n=17) seems very low. Chang et al. report a publication rate for cardiovascular PMA devices of 57% (60/106). During the study period (2000-2004), the FDA approved 216 new PMA devices, which suggests up to 100+ trials should have appeared in the literature. Even if some of these are excluded due to studies published before 2000 or after 2004, and even if there are varying rates of publication in non-cardiovascular specialties, there is still quite a big gap between the authors' figure and the back-of-the-envelope calculation above. To validate their search strategy, the authors could cross-check their results against 1 or 2 years-worth of PMA approvals (i.e., take the ~50 PMA devices approved in 2002, search each for publications, and determine whether any were missed)

MINOR COMMENTS

4. I would suggest revising the title, which currently does not convey the key aim or results of the study (in particular making clear the focus was early / first human clinical testing)

5. Page 7, line 112 – suggest rephrasing to emphasize that the US has a central regulatory body for premarket device review, whereas the EU and other jurisdictions lack such authority

6. Page 7, line 121 – an important caveat is that other studies have pointed to the importance of academic and public-sector research in transformative drug therapies. See Stevens et al. (NEJM 2011;364:535) and Kesselheim et al. (Health Aff 2015;34:286)

7. Page 8, line 142 – there needs to be more information on how the academic / industry tag or "relationship" was determined. Was it on the basis of affiliation only, any financial disclosure, provision of the device/intervention, or some combination of the above? (repeated for page 9, line 179; page 13, line 290)

8. Page 10, line 192 – I presume the authors also checked search engines and other public sources since some devices may have been discontinued, withdrawn, or recalled and would not currently appear in the FDA database

9. The Results section was somewhat difficult to follow, and the presentation of the findings in this section did not seem to mirror the findings highlighted in the abstract or Discussion. I'd recommend reorganizing around the key points

10. Page 10, line 207 – the most frequent journals of publication seemed much less relevant (and could be moved to an appendix) than the most frequent therapeutic areas (cardiovascular, orthopedic, general / plastic surgery, as shown in Table 1)

11. Page 11, line 217 – should the denominators here be 99 instead of 218?

12. Page 11, line 217 – what was the range of approval years, or when was the latest approval for one of the studied devices?

13. Page 11, line 219 – what was the lag between approval and publication specifically for the 43 devices that were approved before any clinical studies?

14. Page 11, line 222 – do you mean "approved / cleared by FDA"? the use of "translation" and "approval" interchangeably here, and elsewhere in the manuscript, is confusing, and if this terminology is retained, it should be better defined upfront

15. Page 12, line 245 – the IDEAL model could be explained for readers unfamiliar with this concept

16. Page 12, line 258 – I am not convinced that this paper could be read-across to the Contopoulos-Ioannidis paper, which appears primarily to include preclinical research (vs. the exclusively in-human studies included here). This would bias the current results to a higher % resulting in approved products relative to the C_I paper

17. References – I would recommend strengthening the references list. The BMJ has published quite a bit recently on devices and transparency, for example, and most of those studies are not cited. Other suggestions are listed above

18. Table 2 – percentages / p-values for the tests reported in Results would be helpful here

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 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:

Information for submitting a revision

Deadline: Your revised manuscript should be returned within one month.

How to submit your revised article: Log into http://mc.manuscriptcentral.com/bmj and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s). As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation 'Revised Manuscript Marked copy'. Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision. Please include these items in the revised manuscript to comply with BMJ style (see: http://www.bmj.com/about-bmj/resources-authors/article-submission/article-requirements and http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists).

Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

1. What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

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.)

3. Patient confidentiality forms when appropriate (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality).

4. Competing interests statement (see http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests)

5. Contributorship statement+ guarantor (see http://resources.bmj.com/bmj/authors/article-submission/authorship-contributorship)

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8. Data sharing statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research)

9. Funding statement and statement of the independence of researchers from funders (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements).

10. Patient involvement statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research).

11. Please ensure the paper complies with The BMJ's style, as detailed below:

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.

e. Results: Please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

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.)
ii. For a cohort study: Absolute event rates over time (eg 10 years) among exposed and non-exposed groups; RRR (relative risk reduction.)
iii. For a case control study:OR (odds ratio) for strength of association between exposure and outcome.
iv. For a study of a diagnostic test: Sensitivity and specificity; PPV and NPV (positive and negative predictive values.)
v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

f. Discussion: To minimise the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vi) unanswered questions and future research

g. Footnotes and statements

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must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.

Date Sent: 29-Mar-2016