Dear Dr. Lurie

Manuscript ID BMJ.2014.023990 entitled "Comparison of the Content of FDA Letters Not Approving Applications for New Drugs and Associated Sponsor Press Releases"

Thank you for sending us this paper, which we were pleased to have the chance to consider and enjoyed reading. 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. This is 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 committee meeting, so that we will be in a better position to understand your study and to decide whether The BMJ is the right journal for it.

Many thanks again. We look forward to seeing your revised article within a month and, we hope, to reaching a decision.

**THE REPORT FROM THE MANUSCRIPT COMMITTEE MEETING, REVIEWERS’ REPORTS, AND THE BMJ’S GENERAL REQUIREMENTS FOR RESEARCH PAPERS ARE AVAILABLE AT THE END OF THIS LETTER.**

First, however, please read these four important points about sending your revised paper back to us:

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

2. Online and print publication: All original research in The BMJ is published with open access. The full text online version of your article, if accepted after revision, will be the indexed citable version (full details are at http://resources.bmj.com/bmj/about-bmj/the-bmjs-publishing-model), while the print and iPad BMJ will carry an abridged version of your article, usually a few weeks afterwards. This abridged version of the article is essentially an evidence abstract called BMJ pico, which we would like you to write using a template and then email it to papersadmin@bmj.com (there are more details below on how to write this using a template). Publication of research on bmj.com is definitive and is not simply interim “epublication ahead of print”, so if you do not wish to abridge your article using BMJ pico, you will be able to opt for online only publication. Please let us know if you would prefer this option.

If/when your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes, and based on the information in your paper’s BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and should not stray beyond the data.

3. Open access publication fee: The BMJ is committed to keeping research articles Open Access (with Creative Commons licences and deposit of the full text content in PubMedCentral as well as fully Open Access on bmj.com). To support this we are now asking all authors to pay an Open Access fee of £3000 on acceptance of their paper. If we accept your article we will ask you to pay the Open Access publication fee; we do have a waiver policy for authors who cannot pay. Consideration of your paper is not related to whether you can or cannot pay the fee (the editors will be unaware of this), and you need do nothing now.

How to submit your revised article: Log into https://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 may also click the below link to start the revision process (or continue the process if you have already started your revision) for your manuscript. If you use the below link you will not be required to login to ScholarOne Manuscripts.

BMJ - Decision on Manuscript ID BMJ.2014.023990
19-Jan-2015
INFORMATION ON REVISING THE CONTENT AND FORMAT OF YOUR ARTICLE

**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: Elizabeth Loder (chair), Tim Cole (statistician), Rebecca Burch, Jose Merino, Georg Roeggla, Tiago Villanueva, Emma Parish, Wim Weber, Anita Jain, Rubin Minhas

Decision: request revisions

Detailed comments from the meeting: The committee was interested in the topic and the underlying ideology of greater transparency. We feel it is important to make people aware about this issue. However, we feel the paper needs to have a more even-handed approach, rather than suggesting that companies issue misleading press-releases.

First and foremost, 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) Please explain the choice of cut-off dates as Aug 11, 2008 to June 27, 2013

2) We would like you to mention in the abstract that CRLs are not made public and also that press releases are not mandatory.

3) Methods - What is the chance that the matching was over-specified - in that they created so many categories - driven from details in the CRLs - that there really wasn't a chance that PRs could match the CRLs on all points?

4) Results: Please share how many statements were made on average per CRL. As CRLs are much longer than press releases, it raises questions about the expectation that a press release could convey as much information as a CRL. It also raises the question of how many press releases for approved drugs mentioned the negative information and other caveats in approval letters.

5) Please share how many of the new molecular entities were rejected with a CRL are now approved and on the market.

6) The methods section may be made clearer and abbreviations are to be avoided.

7) We would like you to reduce the length of the paper and adopt a more even-handed approach in the tone of the paper. Currently the paper seems to suggest that sponsors are manipulating by issuing
misleading press releases. However, press releases are not mandatory, and the FDA being a public body, one may question why information from the CRLs is not made public. This has patient safety implications. We feel the issue is not that press releases fail to summarize CRLs but that the CRLs are not made public despite the fact that a public agency spent a lot of time and money on the analysis. The reasons for this should be made clearer. The focus might rather be to document the extent to which PRs match CRLs, and to suggest how the process may be made more transparent.

8) Some companies might go off and reformulate drugs or do additional things to try to gain approval, and do not want competitors to know details while they are doing that. These letters are not necessarily the end of the development story for all of these drugs or classes of drugs. But the arguments for this should be made clearer.

IMPORTANT
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.

a. In your response to the reviewers and committee please provide, point by point, your replies to the comments made by the reviewers and the editors, and please explain how you have dealt with them in the paper. It may not be possible to respond in detail to all these points in the paper itself, so please do so in the box provided

b. If your article is accepted it will then be edited, proofed, and - after your approval - published on bmj.com with open access. This open access Online First article will not be a pre-print. It will represent the full, citable, publication of that article. The citation will be year, volume, elocator (a unique identifier for that article): eg BMJ 2008;337:a145 — and this is what will appear immediately in Medline, PubMed, and other bibliographical indexes. We will give this citation in print and online, and you will need to use it when you cite your article.

c. Please write an abridged version of the article for the print and iPad BMJ using the appropriate BMJ pico template for your study's design. Please be reassured that it doesn't take long to complete this. When your BMJ pico is ready please email it to papersadmin@bmjgroup.com. The templates for you to download are at http://resources.bmj.com/bmj/authors/bmj-pico

d. Please include these items in the revised manuscript to comply with BMJ style:

**Title**: this should include the study design eg “systematic review and meta-analysis”

**Abstract**
structured abstract including 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 study registration number and name of register – in the last line of the structured abstract.

**Introduction**
this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

**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

**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/

**summary statistics to clarify your message. Please include in the results section of your structured abstract (and, of course, in the article’s results section) the following terms, as appropriate:**
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)

For a cohort study:
• Absolute event rates over time (eg 10 years) among exposed and non-exposed groups
• RRR (relative risk reduction)

For a case control study:
• OR (odds ratio) for strength of association between exposure and outcome

For a study of a diagnostic test:
• Sensitivity and specificity
• PPV and NPV (positive and negative predictive values)
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

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

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

ID of ethics committee approval and name of the ethics committee/IRB; or a statement that approval was not required (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines) and a statement that participants gave informed consent before taking part

a statement that any identifiable patients have provided their signed consent to publication. Please submit, as a supplemental file, the signed BMJ patient consent form giving consent to publication in The BMJ of any information about identifiable individual patients. Publication of any personal information about a patient in The BMJ, for example in a case report or clinical photograph, will normally require the signed consent of the patient.

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signed patient consent form(s), if the article gives enough personal information about any patient(s): this sometimes occurs even in research papers - for example in a table giving demographic and clinical information about a small subgroup in a trial or observational study, or in quotes/tables in a qualitative study - (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality)
a data sharing statement declaring what further information and data you are willing to make available, over and above the results reported in the paper. Suggested wording: "Data sharing: technical appendix, statistical code, and dataset [state whether any patient level data have been anonymised] are available at this repository or website OR from the corresponding author at ". If there are no such further data available, please use this wording: "Data sharing: no additional data available". For papers reporting the main results of trials of drugs or devices we require that the authors state, at a minimum, that the relevant anonymised patient level data are available on reasonable request from the authors.

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for studies funded or sponsored by industry (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)

a statement describing the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

assurance, in the cover letter, that a clinical trial funded by a pharmaceutical or other commercial company follows the guidelines on good publication practice (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)

inclusion in the list of contributors the name(s) any professional medical writer(s), specifying in the formal funding statement for the article who paid the writer. Writers and authors must have access to relevant data while writing articles.

Patient centred research

for studies that are relevant to patients we expect authors to report in their articles the extent of their study’s patient-centredness, as highlighted by these questions:

did you involve patients/service users/carers/lay people in the design of this study? Please state whether you did, and give details (Methods section)

was the development and/or selection of outcome measures informed by patients’ priorities and experiences? Please give details (Methods section)

were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)

have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)

are patients thanked in the contributorship statement or acknowledgements?

for articles reporting randomised controlled trials: did you assess the burden of the intervention on patients’ quality of life and health? If so, what evaluation method did you use, and what did you find? (Methods and Results sections)

REFEREES COMMENTS

Reviewer: 1

Recommendation:

Comments:

This qualitative analysis compared the content of FDA complete response letters related to unapproved applications with the content of press releases emerging from the drug sponsors related to those CRLs. This is an important and unique analysis. The study arrives at the novel, interesting, and valuable finding that sponsor press releases do not match up well with the information in the CRL and poorly transmit the essential details to the public. I strongly support its publication in BMJ, but have a few comments that the authors might consider in the revision process.

1. The authors should make a stronger public health case as to why the information in the CRL is useful and needs to be faithfully reported to the public (rather than simply its financial implications for investors). This isn't just about misleading a few mutual fund managers, but has real implications for patients. Because the CRLs are not routinely publicly disclosed, researchers, patients, physicians, and public health advocates are often left in the dark about non-approval decisions related to investigational drugs. The information in the CRL can be immediately clinically relevant if, for example, a structurally similar drug is currently in use and relevant safety signals are found in the application or
if there are patients using the drug through 'expanded access' protocols or in other countries. Since the CRLs are treated as confidential based on an unnecessarily expansive definition of trade secrecy, the PRs are the only way the public can know what's in them, so this study's documentation of these deficiencies is a great service to the health care community.

2. Along those lines, I would ask the authors to go beyond simply documenting a problem. The authors should suggest specific steps forward so that the problem identified can be remedied. Does the DOJ or SEC need to investigate whether these misleading PRs were intentional and what their material impact was? The paragraph, for example, on transparency in the Discussion is not precise enough--can the FDA now act to improve transparency as the authors suggest? Will this require N&C rulemaking? Does Congress need to get involved?

3. I found the Results section a bit hard to follow. I would recommend subsections to help orient the reader, since the denominator changes a lot among your various analyses. There were some analyses that were superfluous like whether NDAs vs BLAs were more likely to have PRs (who cares?). It's also not clear why having "at least one matching PR statement" is a relevant comparison. I was confused by the 11 PR statements that did not occur in CRLs -- what does that mean, and is that relevant, particularly if the PR was intended to provide information about other stuff as well as the CRL? Similarly, is it relevant that 27/50 PRs don't explicitly state that marketing cannot commence? One would think that is pretty obvious. It might be worthwhile to streamline some of the data presentation so that your essential, powerful message isn't lost among some less meaningful information that you collected along the way.

4. It would be extremely helpful, and I think would make the paper even more powerful, to present examples or quotes from the PR and CRLs. You do this once in the Discussion, omitting the drug names, but since the PRs are not CCI, I would think that would give you license to create a table of PR statements with a second column providing your interpretation about whether these statements were in the CRL, or did not match, or whatever. It would also be useful to provide more redacted CRL statements, if you indeed feel like they should be redacted. Arguably, if a company is issuing a PR about the information in a CRL, doesn't that mean that the company doesn't think that the information is protected, and would give you license to show examples of matching vs. non-matching statements in another qualitative-style table?

Overall, congratulations on an excellent study, which should have a very wide-ranging impact on the field.

Additional Questions:
Please enter your name: Aaron Kesselheim
Job Title: Associate Professor of Medicine
Institution: Harvard Medical School/Brigham and Women's Hospital
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 have received research funding grants from the FDA Office of Generic Drugs and Communication in the past 2 years.

Reviewer: 2
Recommendation:

Comments:
This paper offers a descriptive statistical analysis of complete response letters and associated press releases. The very important finding that emerges is that there is a mismatch between the CRL and the PR, one that may have important public health implications. The dataset is a novel and interesting one and I generally think the paper should be published.

That said, the analysis of statistical differences has a few important weaknesses. The one statistically significant difference reported by the authors concerns the size of firm (p 9, line 53, to page 10). Yet I am concerned that the "finding" here may be an artifact of how the variable was binarized. Put simply, choosing 750 employees as the cutoff separating larger from smaller sponsors seems odd and is never justified. In order for this result to be at all credible, two things must be supplied. First, a prima facie justification for the 750-person cutoff. Second, a robustness check that tells us whether the finding is still significant when the cutoff is 500, or 900, or 1000, or something else. Far superior to these, in my opinion, would be an analysis using the log of the employees variable, as it would exploit the monotonicity required by the hypothesis.

Relatedly, the authors test a number of hypotheses in these differences, and it is not clear whether the reported differences satisfy a Bonferroni-like correction.

Finally, one policy issue raised by this paper is why the FDA or another public health organization cannot do more to publicize the CRLs. I assume that this is a trade information restriction (exemption to FOIA), but I have not kept up with the latest regs on this. The answer to this question would seem to have great weight for the question of "where to go from here."

Additional Questions:
Please enter your name: Daniel Carpenter
Job Title: Freed Professor of Government
Institution: Harvard University
Reimbursement for attending a symposium?: No
A fee for speaking?: No
A fee for organising education?: No
Funds for research?: No
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END
19-Jan-2015