PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pivotal Clinical Trials of Novel Ophthalmic Drugs and Medical Devices: Retrospective Observational Study, 2002-2012
AUTHORS	Hwang, Jenny; Hwang, Thomas; Ciolino, Joseph

VERSION 1 - REVIEW

REVIEWER	Diana Zuckerman National Center for Health Research USA
REVIEW RETURNED	16-Apr-2015

GENERAL COMMENTS	This is an important topic for all physicians and particularly ophthalmologists, but the manuscript would be more informative if several additional questions had been asked and answered. And, given the BMJ audience, a more global overview in the lit review and the discussion would seem more suitable, For those reasons, I would like to see this article published after some improvements. Meanwhile, it was difficult to answer several of the ratings in terms of "yes" and "no." Background: Despite analyzing almost twice the number of devices as drugs, most of the background focused on drugs. Most readers would benefit from more information contrasting the drug approval process vs the device approval process, and would provide insight into the trial differences discussed in the results and discussion section. Methods: The size of the sample and the type of comparison sample are both important, but the availability of relevant comparators wasn't clearly addressed in the manuscript. In addition to the study design issues presented, were the results of the pivotal studies clinically meaningful as well as statistically significant? How adequate were the pivotal studies in measuring risks as well a potential ben Why did the authors restrict themselves to such a small amount of information – additional parameters that would have been interesting might include total # of clinical trials for each drug/device, length of treatment/follow-up in the pivotal study, race/ethnicity/gender/age percentages, what subgroup analyses were performed (if any). Results/Discussion : It is unclear at times if the information being presented is specific to this study/the ophthalmologic field/general information. No subpopulation information is presented, despite talking of the importance of it for clinical decision-making earlier in the paper. The authors' review of the shift from premarket to post-market

	evidence of safety and effectiveness was rather skimpy and the risks inherent for patients when FDA relies on post-market studies were not addressed in the lit review or in the discussion/conclusions. This omission seems unfortunate since the authors point out that one of the required post-market studies had not been started yet after 7 years delay. No information was provided about the study designs of post-market studies -- were they adequate to address the questions not answered in the premarket studies? Although the number of post-market studies was small, information about them was worthy of mention In summary, this is an important article that will be informative to many physicians. It could be improved with some additional information, as noted above.

REVIEWER	Derek J Ward NIHR Horizon Scanning Centre School of Health and Population Sciences College of Medical and Dental Sciences University of Birmingham Edgbaston Birmingham, United Kingdom
REVIEW RETURNED	17-Apr-2015

GENERAL COMMENTS	Thank you for the opportunity to review this paper, which adds to the literature in providing a description of the characteristics of the trials that form the basis of drug and device regulatory approval in the field of ophthalmology. I have only a small number of minor suggestions for revision and questions for the authors, as follows: 1. The aims and objectives for this study (and hence the outcome measures of interest) are clearly stated in the abstract, but not repeated in the text; this should be amended. 2. The study uses an assessment of randomisation and blinding/masking to determine the potential for bias (in addition to trial size). There are several validated scales for assessing the risk of bias in RCTs and the authors should justify why their approach was used in preference to one of these scales (e.g. Jadad score). In particular, there is no assessment of the quality of randomisation or trial drop-out rates, which are usually considered very important in this assessment. This should be considered as part of the study description and (later) study strengths and weaknesses. 3. Results para 2 - trypan blue was approved on the basis of a review of published evidence - does this incorporate randomised and appropriate blinded studies? 4. Results para 4 - it would be useful to the reader to understand more fully the justification of regulators in requiring post-approval studies if this information is available (beyond detection of rare AEs). The lack of subsequent published follow-up studies could then be put in better context. 5. Discussion para 2 - the choice of study to illustrate the high rates

	of response to sham surgery or placebo is taken from a different field of practice - this would be more compelling if it drew directly from pivotal studies identified in this work and could be more easily related directly to ophthalmology. 6. Discussion para 4 - from the readers perspective, one of the key issues is the absence of follow-up studies required by the regulator (or inadequate reporting of such studies). The implications of this finding would benefit from further elaboration.

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1

3. Reviewer 1: “This is an important topic for all physicians and particularly ophthalmologists, but the manuscript would be more informative if several additional questions had been asked and answered. And, given the BMJ audience, a more global overview in the lit review and the discussion would seem more suitable. For these reasons, I would like to see this article published after some improvements.”

Authors’ Response: We thank the reviewer for these comments. As suggested, we have substantially revised the Discussion section to reflect the journal’s global reach, including mention of ongoing device regulation reform efforts in Europe (Discussion, paragraph 5).

4. Reviewer 1: “Despite analyzing almost twice the number of devices as drugs, most of the background focused on drugs. Most readers would benefit from more information contrasting the drug approval process vs the device approval process, and would provide insight into the trial differences discussed in the results and discussion section.”

Authors’ Response: As suggested, we have revised the Discussion section to provide more information to readers on the differences in regulatory standards between drugs and devices. In particular, Discussion paragraph 5 highlights the implications of our findings to that ongoing debate (Discussion, paragraph 5).

5. Reviewer 1: “The size of the sample and the type of comparison sample are both important, but the availability of relevant comparators wasn’t clearly addressed in the manuscript. In addition to the study design issues presented, were the results of the pivotal studies clinically meaningful as well as statistically significant? How adequate were the pivotal studies in measuring risks as well as potential benefits? Why did the authors restrict themselves to such a small amount of information – additional parameters that would have been interesting might include total # of clinical trials for each drug/device, length of treatment/follow-up in the pivotal study, race/ethnicity/gender/age percentages, what subgroup analyses were performed (if any)”

Authors’ Response: We thank the review for the helpful comment. As suggested, and within the scope of our study and time frame for the revision, we have added the following to the Results: (i) number of clinical trials for each drug/device; (ii) which subgroup analyses were performed; and (iii) further information on the post-approval studies (Results, paragraphs 2-4). We have also addressed and incorporated these additional data into the Discussion (Discussion, paragraphs 1-2 and 4). We agree with the reviewer that further transparency into the evidentiary standards underpinning the approvals of new therapeutics is warranted. While outside the scope of this study, we believe such analysis deserves further exploration.

6. Reviewer 1: “It is unclear at times if the information being presented is specific to this study/the

ophthalmologic field/general information. No subpopulation information is presented, despite talking of the importance of it for clinical decision-making earlier in the paper."

Authors' Response: As suggested, we have included additional data on subgroup analyses (see response to comment #5 above) and have also incorporated this information in the Discussion (Discussion, paragraphs 1-2). We have also revised the commentary in the Discussion to more clearly articulate how our results may inform specialists in the field as well as broader policy debates (e.g., Discussion, paragraphs 2 and 4).

7. Reviewer 1: "The authors' review of the shift from premarket to post-market evidence of safety and effectiveness was rather skimpy and the risks inherent for patients when FDA relies on post-market studies were not addressed in the lit review or in the discussion/conclusions. This omission seems unfortunate since the authors point out that one of the required post-market studies had not been started yet after 7 years delay."

Authors' Response: We thank the reviewer for the comment, and we agree that the Discussion would benefit from greater emphasis on the importance of post-market studies. As suggested, we have substantially revised the Discussion and incorporated new text to address this comment, in particularly Discussion paragraph 2, in which we more clearly articulate the risks to patients, and paragraphs 3 and 4 (Discussion, paragraphs 2-4).

8. Reviewer 1: "No information was provided about the study designs of post-market studies – were they adequate to address the questions not answered in the premarket studies? Although the number of post-market studies was small, information about them was worthy of mention"

Authors' Response: We thank the reviewer for the comment. As suggested, we have included additional information on the required post-approval studies in both the Results and Discussion section (Results, paragraph 4; Discussion, paragraphs 3-4). In our commentary, we point out that the transparency of the post-approval trial design and results should be radically improved.

9. Reviewer 1: "In summary, this is an important article that will be informative to many physicians. It could be improved with some additional information, as noted above."

Authors' Response: We thank the reviewer for the helpful comments.

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REVIEWER 2

10. Reviewer 2: "Thank you for the opportunity to review this paper, which adds to the literature in providing a description of the characteristics of the trials that form the basis of the drug and device regulatory approval in the field of ophthalmology. I have only a small number of minor suggestions for revision and questions for the authors."

Authors' Response: We thank the reviewer for these comments.

11. Reviewer 2: "The aims and objectives for this study (and hence the outcome measures of interest) are clearly stated in the abstract, but not repeated in the text; this should be amended."

Authors' Response: As suggested, we have aligned the text to the Abstract, including clearly stating the objectives of the study and the endpoints of interest (Introduction, paragraph 4; Methods, paragraph 4).

12. Reviewer 2: “The study uses an assessment of randomisation and blinding/masking to determine the potential for bias (in addition to trial size). There are several validated scales for assessing the risk of bias in RCTs and the authors should justify why their approach was used in preference to one of these scales (e.g., Jadad score). In particular, there is no assessment of the quality of randomisation or trial drop-out rates, which are usually considered very important in this assessment. This should be considered as part of the study description and (later) study strengths and weaknesses.”

Authors’ Response: We thank the reviewer for the comment. We refer to the response to comment #1 above, and have incorporated mention of this point in the “Strengths and limitations” section of the Discussion (Discussion, paragraph 6).

13. Reviewer 2: “Results para 2 – trypan blue was approved on the basis of a review of published evidence – does this incorporate randomised and appropriate blinded studies?”

Authors’ Response: We have added mention of the published evidence reviewed for the approval of trypan blue (Results, paragraph 2). None of those studies were randomized or controlled.

14. Reviewer 2: “Results para 4 – it would be useful to the reader to understand more fully the justification of regulators in requiring post-approval studies if this information is available (beyond detection of rare AEs). The lack of subsequent published follow-up studies could then be put in better context.”

Authors’ Response: As suggested, we have provided additional language in paragraph 3 of the Discussion to better convey the importance and justification of mandating post-approval studies. We have included mention of a vagus nerve stimulator, whose post-approval study led to changes in labeling of the device’s efficacy, as well as the case of a registry of metal-on-metal hip implants (Discussion, paragraph 3).

15. Reviewer 2: “Discussion para 2 – the choice of study to illustrate the high rates of response to sham surgery or placebo is taken from a different field of practice – this would be more compelling if it drew directly from pivotal studies identified in this work and could be more easily related directly to ophthalmology.”

Authors’ Response: We agree with the reviewer, and, as suggested, have added a new reference (ref#25) documenting high rates of placebo response in ophthalmological trials.

16. Reviewer 2: “Discussion para 4 – from the readers perspective, one of the key issues is the absence of follow-up studies required by the regulator (or inadequate reporting of such studies). The implications of this finding would benefit from further elaboration.”

Authors’ Response: We thank the reviewer for this comment. As suggested, and with reference to comments #7 and #14, we substantially revised the Discussion and incorporated new text to better articulate the importance of post-approval trials.