PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The safety of intravitreal bevacizumab monotherapy in adult ophthalmic conditions: systematic review
AUTHORS	Poku, Edith; Rathbone, John; Wong, Ruth; Everson-Hock, Emma; Essat, Munira; Pandor, Abdullah; Wailoo, Allan

VERSION 1 - REVIEW

REVIEWER	Katie Saunders Cambridge Centre for Health Services Research, UK
REVIEW RETURNED	11-Apr-2014

GENERAL COMMENTS	**The safety of intravitreal bevacizumab monotherapy in ophthalmic conditions: a systematic review** The methods used in this paper are appropriate. It is a systematic review of safety events associated with treatment. The paper addresses 3 research questions 1) What are the safety events associated with IVB use 2) What is the difference in safety adverse events with IVB compared with other agents and 3) What is the evidence about the association between IVB injection quality and safety The paper reads in a slightly confused way as the results and conclusion section of the abstract focus on research question 3 (the lack of evidence about the association between injection quality and safety) but this point is not mentioned specifically in the main paper methods or results sections at all. The methods needed to answer each of the three research questions may be slightly different and could be clarified throughout. Comments about safety events associated with IVB use may be answered from considering the IVB arm of trials with comparison arms instead of just focusing on the results from the main RCT comparisons. The main concern about this work is that the search strategy only runs until 2012. The authors cite three important recent papers in their discussion (97-99) but do not include them in the review – as commented below some of the results from figure 2 have been previously published in a more updated form.

Search strategy

The search strategy appears appropriate.

Did the search include registers of trials such as clinical trials.gov or the EU clinical trials register? – or other sources of safety event reporting. This should be stated.

Data extraction

How were the outcomes of interest decided? (page 4 line 37 onwards)

Risk of bias

This is done appropriately

Statistical analysis

The authors do not attempt to perform a meta-analysis for the observational studies identified but do include a summary table (table 3) with details of adverse events reported from each study. This approach is appropriate.

The only statistical analysis presented is a meta-analysis of the safety events from the CATT and IVAN trials (2 RCTs). (comparison of IVB with an alternative agent).

Results

Reference 97 (included in the discussion but not the results synthesis) presents these meta-analysis results from sections 3.1.1, 3.1.2 and 3.1.3 of figure 2 in an already published form (the ref 97 version includes results from the two year IVAN results, while figure 2 in this paper includes only 1 year IVAN results, ref 97 could be considered more up to date).

As mentioned above the results could be clarified with respect to the three research questions mentioned by the study authors.

1) Is this study more interested in review of the safety events of intravitreal bevacizumab without comparator groups or 2) is this review interested in the head to head comparison of safety of IVB with other agents ?

If the answer is 1) then including the safety event information from the 22 RCTs for the IVB arm alone in a summary table in the similar way table 3 for observational studies would be appropriate or if it is 2) then including lines 3-31 from page 7 in tabular form (narrative summary of comparison of safety events from the 22 RCTs) might highlight this section of results.

REVIEWER	Mr Christopher Brand Royal Hallamshire Hospital Sheffield UK Declarations of interest: I have previously worked with the School of Health and Related Research (ScHARR) , University of Sheffield on research projects. I was contacted concerning possible research project involving intra-vitreal bevacizumab by ScHARR ; I do not know if it was related to this study project. I have received remuneration from Novartis Pharmaceuticals UK Ltd and Pfizer UK for advisory board work. I have also been involved in research for both of these companies into the treatment of wet age related macular degeneration and diabetic macular oedema.
REVIEW RETURNED	23-Apr-2014

GENERAL COMMENTS	This paper is an excellent presentation. However, the results are not novel. This paper will be published, the question is which journal? 1.TITLE: The safety of intra-vitreal bevacizumab monotherapy in ophthalmic conditions: systematic review. Why has the use on intra-vitreal bevacizumab in retinopathy of prematurity not been included? If this study is related to an adult only population the title should perhaps be amended accordingly. 2.Methodology: Why were the electronic searches for studies limited to January 2009 to May 2012? 3.Results: Twenty-two randomised controlled trials (RCTs) and 67 observational studies were included. Only 2 RCTs reported valid safety data. It appears from the text in your paper that the 2 RCT's of good quality are the CATT and IVAN trial data; the study quality of the observational trials was difficult to assess I gather. Did you search for safety data on the effects of intra-vitreal bevacizumab on patients with wet AMD, drawing comparisons to age matched controls from the public health publications who were not receiving injections. Eg risk of CVA, MI, death rates? In addition to comparisons with intra-vitreal ranibizumab in studies such as CATT and IVAN. 4.Conclusion: Current evidence demonstrates low rates of serious local and systemic adverse events following IVB in a number of ophthalmic conditions. However, the role of IVB quality in the incidence of adverse events remains unclear. Retina. 2011 Sep;31(8):1449-69. A systematic review of the adverse events of intravitreal anti-vascular endothelial growth factor injections. Curr Opin Ophthalmol. 2009 May;20(3):223-5.. Safety and efficacy of intravitreal anti-VEGF injections for age-related macular degeneration. Curr Med Res Opin. 2011 Jul;27(7):1465-75.

	A systematic review of the efficacy and safety outcomes of anti-VEGF agents used for treating neovascular age-related macular degeneration: comparison of ranibizumab and bevacizumab. Given the aforementioned papers that are available in peer review journals. Do you think your paper offers any further information? It appears to me that the only evidence your paper offers in addition to the other similar publications are the findings from the CATT and IVAN trial. 5.Introduction: In the UK, Ranibizumab is licensed for the treatment of wet AMD, diabetic macular oedema and oedema secondary to retinal vein occlusion. The cost of £742.17 per injection (0.23 ml per vial) is the costing from the British National Formulary. In the UK, 'Patient Access Schemes' are offered by most manufacturers where NICE are seeking assurance of value for money of a newly launched project. Novartis have offered a 'patient access scheme' for Ranibizumab for all NICE indications in the UK. I am not aware of Macugen being used in any UK department for the treatment of wet AMD. However, bevacizumab is used as an unlicensed intervention in ophthalmic conditions as a comparatively effective but cheaper treatment (£242.66 for 4ml/100mg vial). Annual cost savings of approximately £300m has been estimated if bevacizumab is used as standard treatment instead of ranibizumab in patients with AMD. Although this statement is referenced in the paper, it is a throw away sentence which grabs headlines but needs greater explanation. There are no real concerns over the effectiveness and safety of intra-vitreal Ranibizumab. The continued debate over intra-vitreal Bevacizumab is related to the price and safety in comparison to Ranibizumab. What are the costs of a dispensing pharmacist dividing vials of Bevacizumab for intra-ocular use? Bevacizumab is unlicensed: What are the expected costs of obtaining a licence for Bevacizumab for intra-ocular use? If Bevacizumab had a licence for intra-ocular use, what would be the price per vial for intra-ocular use? If unlicensed Bevacizumab is continually proposed as a comparator in the treatment of AMD, DMO and macular oedema secondary to RVO will newer treatments never become available? Is the licensing process of drugs not present for a purpose? 6.In summary: The methodology and presentation of this paper is excellent. However, the findings are not novel and very similar to previous publications on this subject. The only new data you present appears to be related to the CATT and IVAN trials. This paper is worthy of publication, the question is which journal. I will leave it to the editorial team to decide if they think this paper warrants publication in BMJ open.

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1: KATIE SAUNDERS
INSTITUTION AND COUNTRY CAMBRIDGE CENTRE FOR HEALTH SERVICES RESEARCH, UK
The paper addresses 3 research questions

1) What are the safety events associated with IVB use
2) What is the difference in safety adverse events with IVB compared with other agents and
3) What is the evidence about the association between IVB injection quality and safety

The paper reads in a slightly confused way as the results and conclusion section of the abstract focus on research question 3 (the lack of evidence about the association between injection quality and safety) but this point is not mentioned specifically in the main paper methods or results sections at all.

RESPONSE: We agree that information about the relationship between adverse events and injection was not specifically mentioned in the methods, although we sought to evaluate the relationship based on available data. The methods section has been revised as follows:
'Information abstracted included study characteristics, participant details (e.g. number of patients, eye condition, mean age, and baseline comparability), intervention and comparator details (e.g. source, dose, injection quality and frequency of treatment) and outcomes'

The methods needed to answer each of the three research questions may be slightly different and could be clarified throughout. Comments about safety events associated with IVB use may be answered from considering the IVB arm of trials with comparison arms instead of just focusing on the results from the main RCT comparisons.

RESPONSE: We agree with the comments in relation to providing answers to three separate research questions as outlined. However, we are certain that the approach to data extraction was appropriate to provide possible answers to these questions. Our plan to undertake pooled analyses and sub-group analyses was limited by available data due to incomplete reporting or heterogeneity in relevant studies. Additionally, comparative studies addressing safety of interventions need additional criteria, such as follow-up period greater than 6 months, definition of adverse events (AEs) and description of method of ascertaining AEs for evaluation of validity. Most studies did not report on these items. We considered that it was more appropriate to report mainly on those studies that provided valid safety data. Thus, we considered that the most robust outcomes to present were those of the CATT and IVAN which were large, well-conducted studies. However, to provide additional information, we also described outcomes for other RCTs comparing intravitreal bevacizumab to other treatments including pegaptinib, triamcinolone, sham injection [lines 3 to 8 of page 7 of 44].

Information about the relationship between injection quality and adverse events was presented in the Results section as follows:
'There were limited data to assess quality of administered IVB.' (Line 24 and 25 of page6 of 44)

In addition, we included additional information in APPENDIX 10: ADVERSE EVENT RATES FROM OBSERVATIONAL STUDIES, in Table A 14: Ocular adverse events in included observational studies

In the column, designated, 'Notes', we noted that,
'Authors reported that two eyes developed chemosis at the injection site one day after IVB that resolved with a topical steroid treatment in one week. One eye developed a retinal detachment two months after IVB; however, the relationship between IVB and the detachment was questionable'. [Ikuno 2009] (Line 40 of page 30 of 44)

Furthermore, we reported that,
'Authors reported that there were no adverse events related to IVB nor to the injection procedure.'[Julian 2011] (Line 32 of page 31 of 44)

The main concern about this work is that the search strategy only runs until 2012. The authors cite three important recent papers in their discussion (97-99) but do not include them in the review – as commented below some of the results from figure 2 have been previously published in a more updated form.

RESPONSE: Please refer to our response to Editor's comment relating to updated searches.

Search strategy
The search strategy appears appropriate.Did the search include registers of trials such as clinical trials.gov or the EU clinical trials register? – or other sources of safety event reporting. This should be stated.

RESPONSE: We did not search clinical trial registers for safety outcomes and have included this information in the revised manuscript. We are aware that clinical trials registers might be useful sources of evidence for clinical efficacy data, however clinical trials, in general, are limited in providing safety data due to lack of adequate power or sufficient follow-up periods to evaluate adverse events.

Alternatively, we searched TOXLINE , a comprehensive electronic bibliographic database covering pharmacological, toxicological and biochemical effects of drugs and chemical agents.

Data extraction
How were the outcomes of interest decided? (page 4 line 37 onwards)

RESPONSE: We considered the outcomes of interest based on reported safety events reported in the International intravitreal bevacizumab safety survey, a worldwide survey of international vitreoretinal experts reported by Fung et al. Outcomes of interest were further finalised following consultation with the commissioners of the related project, the National Institute for Health and Care Excellence.

Furthermore, safety data were limited to important and serious adverse events as defined by the Food and Drugs Agency (http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm

Risk of bias
This is done appropriately

RESPONSE: We agree with this comment.

Statistical analysis
The authors do not attempt to perform a meta-analysis for the observational studies identified but do include a summary table (table 3) with details of adverse events reported from each study. This approach is appropriate.

The only statistical analysis presented is a meta-analysis of the safety events from the CATT and IVAN trials (2 RCTs). (comparison of IVB with an alternative agent).

RESPONSE: We agree with this comment.

Results
Reference 97 (included in the discussion but not the results synthesis) presents these meta-analysis results from sections 3.1.1, 3.1.2 and 3.1.3 of figure 2 in an already published form (the ref 97 version includes results from the two year IVAN results, while figure 2 in this paper includes only 1 year IVAN results, ref 97 could be considered more up to date).
As mentioned above the results could be clarified with respect to the three research questions mentioned by the study authors.

1) Is this study more interested in review of the safety events of intravitrealbevacizumab without comparator groups or 2) is this review interested in the head to head comparison of safety of IVB with other agents ?
If the answer is 1) then including the safety event information from the 22 RCTs for the IVB arm alone in a summary table in the similar way table 3 for observational studies would be appropriate or if it is 2) then including lines 3-31 from page 7 in tabular form (narrative summary of comparison of safety events from the 22 RCTs) might highlight this section of results.

RESPONSE:We agree with the comments of reviewer 1.

We considered head-to-head comparisons of the safety of IVB with other agents. We have revised the text in the discussion section to highlight that we were interested in direct comparisons.
For our systematic review of safety, we included randomised controlled trials (RCTs) which compared bevacizumab with laser therapy (n=9), sham injection (n=5), IVT (n=5), IVR (n=4) and pegaptanib (n=2). Calculated relative risks are presented in forest plots and are available in the full report of the project at
http://www.nicedsu.org.uk/Bevacizumab%20report%20%20NICE%20published%20version%2011.04.13.pdf.

Overall, adverse event rates were low or not estimable due to zero events in several bevacizumab and comparators groups. Additionally, most outcomes were not significantly different between treatment groups. We considered that a narrative summary of studies with observable events and a forest plot of RCTs with the most valid safety data would be more useful than presenting a table of all comparative evaluations of included RCTs. We also did not include all comparisons available in the full report due to the number of figures and tables allowed for submission.

REVIEWER 2: MR CHRISTOPHER BRAND, INSTITUTION AND COUNTRY ROYAL HALLAMSHIRE HOSPITAL
SHEFFIELD, UK

1.TITLE: The safety of intra-vitreal bevacizumab monotherapy in ophthalmic conditions: systematic review. Why has the use on intra-vitreal bevacizumab in retinopathy of prematurity not been included? If this study is related to an adult only population the title should perhaps be amended accordingly.

RESPONSE: The study was related to adults with ophthalmic conditions. Therefore, we have revised the title of our manuscript to reflect this more clearly.

2.Methodology: Why were the electronic searches for studies limited to January 2009 to May 2012

RESPONSE: Please refer to our response to Editor’s comment relating to updated searches

3. Results: Twenty-two randomised controlled trials (RCTs) and 67 observational studies were included. Only 2 RCTs reported valid safety data.It appears from the text in your paper that the 2

RCT's of good quality are the CATT and IVAN trial data; the study quality of the observational trials was difficult to assess I gather.

RESPONSE: We agree with this comment.

Did you search for safety data on the effects of intra-vitrealbevacizumab on patients with wet AMD, drawing comparisons to age matched controls from the public health publications who were not receiving injections. Eg risk of CVA, MI, death rates? In addition to comparisons with intra-vitrealranibizumab in studies such as CATT and IVAN.

RESPONSE:We searched for safety data for all adult patients treated with intra-vitreal bevacizumab monotherapy. We included all controlled trials or observational studies including ≥10 participants with reports of adverse events following IVB given as a monotherapy.

4.Conclusion: Current evidence demonstrates low rates of serious local and systemic adverse events following IVB in a number of ophthalmic conditions. However, the role of IVB quality in the incidence of adverse events remains unclear.

Retina. 2011 Sep;31(8):1449-69.
A systematic review of the adverse events of intravitreal anti-vascular endothelial growth factor injections.

CurrOpinOphthalmol. 2009 May;20(3):223-5..
Safety and efficacy of intravitreal anti-VEGF injections for age-related macular degeneration.

Curr Med Res Opin. 2011 Jul;27(7):1465-75.
A systematic review of the efficacy and safety outcomes of anti-VEGF agents used for treating neovascular age-related macular degeneration: comparison of ranibizumab and bevacizumab.

Given the aforementioned papers that are available in peer review journals. Do you think your paper offers any further information? It appears to me that the only evidence your paper offers in addition to the other similar publications are the findings from the CATT and IVAN trial.

RESPONSE: We think that our work provided additional information from the CATT and IVAN (1 year data). It also highlighted existing limitations relating to IVB safety evidence.

5.Introduction:
In the UK, Ranibizumab is licensed for the treatment of wet AMD, diabetic macular oedema and oedema secondary to retinal vein occlusion. The cost of £742.17 per injection (0.23 ml per vial) is the costing from the British National Formulary. In the UK, 'Patient Access Schemes' are offered by most manufacturers where NICE are seeking assurance of value for money of a newly launched project. Novartis have offered a 'patient access scheme' for Ranibizumab for all NICE indications in the UK.I am not aware of Macugen being used in any UK department for the treatment of wet AMD.

RESPONSE: One objective of the commissioned project from which this manuscript was developed, was to estimate the extent of intravitreal bevacizumab (IVB) used in the UK.

We identified documents relating to IVB use in eye conditions in health establishments in the UK. Keyword searching was undertaken within specific databases and web-pages of Primary Care Trusts (PCTs) and National Health Service (NHS) sites in England; local health boards in Wales; Health and Social Care Trusts in Northern Ireland and NHS health boards in Scotland were undertaken. In addition, NHS eye hospital websites via NHS Choices were identified and searched. Searching using

the Google search engine was also undertaken.

A mapping process was adopted to identify the use of bevacizumab in England, Scotland and Wales. Records were considered to contribute data to this evidence base if IVB use was suggested, recommended or supported for the management or treatment of an ophthalmic condition. Retrieved documents were then examined. Relevant data were abstracted.

(1) We noted on a web-link of the Moorfields Eye Hospital,listed treatment options for wet age-related macular degeneration which included Avastin, Macugen and Lucentis.

(2) We also identified the following on the web-page of the Eastern and Coastal Kent PCT:

Policy Recommendation PR007/03: Anti-vascular Endothelial Growth Factors (Anti-VEGFs) for Age-Related Macular Degeneration (AMD)

Summary and recommendations
Photo-dynamic therapy is the recommended first-line treatment for patients with 'classic or predominantly classic sub-types of AMD' in accordance to NICE guidance.

Access to pegatanib treatment based on pre-specified criteria. In the section, entitled – key finding and conclusions – it (was) stated that, 'Lucentis® [ranibizumab] and Macugen® [pegaptanib] are licensed for the treatment of AMD, Avastin® [bevacizumab] is not licensed for use in the treatment of wet AMD, but is used off-label.'

[Issue date: April 2007. Review date: October 2007]

However, as available evidence was obtained from policy-related documents, minutes of board meetings or other unspecified documents, we have revised the introduction section of our manuscript because a statement referring to the use of Macugen in AMD might not imply its use in clinical practice.

However, bevacizumab is used as an unlicensed intervention in ophthalmic conditions as a comparatively effective but cheaper treatment (£242.66 for 4ml/100mg vial). Annual cost savings of approximately £300m has been estimated if bevacizumab is used as standard treatment instead of ranibizumab in patients with AMD.
Although this statement is referenced in the paper, it is a throw away sentence which grabs headlines but needs greater explanation.
There are no real concerns over the effectiveness and safety of intra-vitrealRanibizumab. The continued debate over intra-vitrealBevacizumab is related to the price and safety in comparison to Ranibizumab.

What are the costs of a dispensing pharmacist dividing vials of Bevacizumab for intra-ocular use?
Bevacizumab is unlicensed: What are the expected costs of obtaining a licence for Bevacizumab for intra-ocular use?
If Bevacizumab had a licence for intra-ocular use, what would be the price per vial for intra-ocular use?
If unlicensed Bevacizumab is continually proposed as a comparator in the treatment of AMD, DMO and macular oedema secondary to RVO will newer treatments never become available?
Is the licensing process of drugs not present for a purpose?

RESPONSE: We agree that the continuing debate about the use ofintravitreal bevacizumab (IVB) has been driven by costs and safety issues related to reformulated treatment. The aim of this manuscript

was to present evidence relating to the safety of IVB monotherapy in ophthalmic conditions. We did not conduct any formal cost or economic analysis relating to reformulating process for providing IVB. Therefore, we are unable to provide further information on actual costs of IVB or comment on licensing procedures.

We have revised our text to provide less emphasis on definitive costs of IVB.

6.In summary:
The methodology and presentation of this paper is excellent. However, the findings are not novel and very similar to previous publications on this subject. The only new data you present appears to be related to the CATT and IVAN trials.This paper is worthy of publication, the question is which journal.I will leave it to the editorial team to decide if they think this paper warrants publication in BMJ open.

RESPONSE: We agree with the reviewer's comment and look forward to your further consideration of our manuscript following our revisions.

VERSION 2 – REVIEW

REVIEWER	Katie Saunders Cambridge Centre for Health Services Research
REVIEW RETURNED	05-Jun-2014

GENERAL COMMENTS	I think that the key concerns were not statistical, the methodological quality is high. I also see that it has been reviewed by an opthalmologist who gave a relevant clinical perspective and agreed that the methods were appropriate. The responses to the reviews are clear, and show that the authors have engaged well with the review process and have made appropriate revisions. However they have not updated the search. Their comments and justification here seem reasonable to me but I think that the final decision to accept the revised paper or not should be editorial - methodologically the study is fine (and of a substantially higher quality than most of the papers that I review for BMJ open).