PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-effectiveness of ranibizumab and bevacizumab for age-related macular degeneration: 2-year findings from the IVAN randomised trial
AUTHORS	Dakin, Helen; Wordsworth, Sarah; rogers, chris; Abangma, Giselle; Raftery, James; Harding, Simon; Lotery, Andrew; Downes, Susan; Chakravarthy, Usha; Reeves, Barnaby; on behalf of the, IVAN Study Investigators

VERSION 1 - REVIEW

REVIEWER	David W. Hutton University of Michigan, USA I do not have any competing interests except that I am a researcher who also conducts cost-effectiveness analyses of anti-VEGF therapies for age-related macular degeneration.
REVIEW RETURNED	11-Mar-2014

GENERAL COMMENTS	My concerns about items 11 and 12 relate to two issues not being addressed sufficiently: The current UK price for ranibizumab is not reflected in this analysis. The cost of ranibizumab is a substantial portion of the additional costs. The current price is likely substantially lower than that reported here. The authors could describe more about how this analysis based on IVAN may be different if it were to use data from CATT. Overall: This is a very nice paper. I agree with the authors that, “Unlike previous studies, our analysis is based on high-quality data from an RCT, which was powered to exclude any clinically-meaningful difference in visual acuity and with prospective measurements of costs and quality of life.” My main concern is with the generalizability of some of the conclusions given that this analysis: * seems to be based on an older UK price for ranibizumab * is based on one of several RCT's evaluating ranibizumab and bevacizumab (CATT, GEFAL, MANTA) These are not fatal flaws, but ought to be acknowledged as potential limitations to generalizability. Detailed comments: I have an issue with the third bullet point under “Article Summary”:

	This study is an important contribution to the evaluation of the cost-effectiveness of alternative treatment regimens for nAMD, but it is not the first. For example, see: Raftery J, Clegg A, Jones J, et al. Ranibizumab (Lucentis) versus Bevacizumab (Avastin): modelling cost effectiveness. Br J Ophthalmol 2007;91:1244–6. Patel JJ, Mendes MA, Bounthavong M, et al. Cost-utility analysis of bevacizumab versus ranibizumab in neovascular age-related macular degeneration using a Markov model. J Eval Clin Pract 2012;18:247–55. If the authors wish to say it is the first, this study is the first trial-based CEA of alternative treatment regimens for nAMD (to my knowledge). The paragraph describing this literature in the introduction (middle of page 5) is pretty good. Methods: UK negotiated price for ranibizumab It looks like the price for ranibizumab was from 2011 (citation 4 says September 2011), prior to the updated negotiated price in the patient access scheme: http://www.nice.org.uk/newsroom/pressreleases/DraftGuidanceYesRanibizumabCommonEyeCondition.jsp Although the terms of that agreement are “commercial in confidence”, it would be nice to see a more thorough sensitivity analysis on ranibizumab price. Discussion: The authors may wish to be a little more circumspect in some of the conclusions. These conclusions are based on the IVAN trial experience. This analysis does not use data from CATT or current UK pricing of ranibizumab. Page 15, Lines 23-26: “This study demonstrates that in a UK setting, we can be >99% confident that ranibizumab represents very poor value for money compared with bevacizumab at the £20,000 ($31,000) per QALY ceiling ratio used within NHS decision-making.” Since we do not know that the current UK pricing is representative of the prices used in the IVAN study, it may be more accurate to say, “This study demonstrates that in the setting of the IVAN trial in the UK, we can be >99% confident that ranibizumab represented very poor value for money compared with bevacizumab at the £20,000 ($31,000) per QALY ceiling ratio used within NHS decision-making.” Pages 15 , line 54- page 16, line 4 “CATT and IVAN provide robust data to guide regulators in this decision, demonstrating that ranibizumab and bevacizumab have comparable effects on vision and similar safety profiles,6 7 but that ranibizumab costs £3.5 million per QALY compared with bevacizumab.” I agree with the first part of that sentence. The second part would suggest that the CATT results also suggest that ranibizumab costs £3.5 million per QALY compared with bevacizumab (which this study does not show). I might say something like, “CATT and IVAN provide robust data to guide regulators in this decision, demonstrating that ranibizumab and bevacizumab have comparable effects on vision and similar safety profiles,6 7 but this analysis of IVAN shows that to the extent ranibizumab has better health outcomes, they cost £3.5 million per QALY compared with bevacizumab.” Page 17, lines 51-55:

	"For example, the incidence of SAEs was substantially lower in IVAN than CATT,6 7 although sensitivity analyses suggested that this did not change the conclusions." It's my understanding that the sensitivity analysis performed here examined including the SAE's observed in IVAN. Did the authors also examine SAE rates as high as those observed in CATT? Discussion: It would be good to comment on the relatively short time horizon (presumably, patients with AMD will be receiving these injections for the rest of their lives). I would presume that since the health outcomes seemed very similar between ranibizumab and bevacizumab, and there did not appear to be a trend in year 2, that we would expect these results to hold over a longer time period. The differences between continuous and discontinuous may be more difficult to discern over this 2-year time horizon of analysis.

REVIEWER	Thomas Butt UCL Institute of Ophthalmology University College London United Kingdom TB reports employment from UCB Pharma SA and grants from Notal Vision outside the reviewed work.
REVIEW RETURNED	01-May-2014

GENERAL COMMENTS	The manuscript describes the cost effectiveness of bevacizumab compared with ranibizumab for age-related macular degeneration using cost minimisation analysis and the cost effectiveness of continuous compared with discontinuous treatment using cost-utility analysis. The study is a within trial economic evaluation using the IVAN randomised trial. Minor comments: p4 line 17: I expect there have been evaluations of anti-VEGF vs. vPDT for nAMD, so consider clarifying to "of alternative anti-VEGF treatment regimens" p9 line 6: If possible, please comment on how the not-for-profit NHS provider price per syringe compares with the list price for bevacizumab, allowing for dosing. p10, line 45: Please confirm whether QALYs were also discounted in year 2. p11, line 50: Were 13 discontinuous injections distributed evenly across the two years? If there was a trend upwards or downwards, would this have implications for cost-effectiveness of continuous vs. discontinuous regimens over a longer time horizon. p15 line 2: Please confirm whether the pre-specified non-inferiority margin of 0.05 QALYs (p12) was also met using HUI-3-derived utilities? p15 line 35: Does 17,295 eyes requiring ant-VEGF therapy already include some eyes treated with bevacizumab? If so, the estimated saving from switiching may be lower Time horizon: the use of a two-year time horizon for an economic evaluation of a chronic condition warrants some discussion.

	Text: p3 line 9: abbreviate NHS p3 line 51: consider revising 'little/no' to one or the other p5 line 14: £742/dose in the UK p9 line 45: abbreviate ETDRS p12 line 8: expand FFA

VERSION 1 – AUTHOR RESPONSE

Reviewer Name David W. Hutton
Institution and Country University of Michigan, USA

My concerns about items 11 and 12 relate to two issues not being addressed sufficiently:
The current UK price for ranibizumab is not reflected in this analysis. The cost of ranibizumab is a substantial portion of the additional costs. The current price is likely substantially lower than that reported here.
The authors could describe more about how this analysis based on IVAN may be different if it were to use data from CATT.
We have addressed these comments below.

Overall:

This is a very nice paper.
I agree with the authors that, “Unlike previous studies, our analysis is based on high-quality data from an RCT, which was powered to exclude any clinically-meaningful difference in visual acuity and with prospective measurements of costs and quality of life.”

My main concern is with the generalizability of some of the conclusions given that this analysis:
* seems to be based on an older UK price for ranibizumab
* is based on one of several RCT's evaluating ranibizumab and bevacizumab (CATT, GEFAL, MANTA)
These are not fatal flaws, but ought to be acknowledged as potential limitations to generalizability.
RESPONSE: We have addressed these comments below.

Detailed comments:

I have an issue with the third bullet point under “Article Summary”:
This study is an important contribution to the evaluation of the cost-effectiveness of alternative treatment regimens for nAMD, but it is not the first.
For example, see:
Raftery J, Clegg A, Jones J, et al. Ranibizumab (Lucentis) versus Bevacizumab (Avastin): modelling cost effectiveness. Br J Ophthalmol 2007;91:1244–6.
Patel JJ, Mendes MA, Bounthavong M, et al. Cost-utility analysis of bevacizumab versus ranibizumab in neovascular age-related macular degeneration using a Markov model. J Eval Clin Pract 2012;18:247–55.
If the authors wish to say it is the first, this study is the first trial-based CEA of alternative treatment regimens for nAMD (to my knowledge).
The paragraph describing this literature in the introduction (middle of page 5) is pretty good.
RESPONSE: In response to this comment and a comment by Reviewer 2, we have revised this sentence to read “Our study is the first trial-based economic evaluation to evaluate the cost-effectiveness of alternative anti-VEGF treatment regimens for nAMD.”

Methods:

UK negotiated price for ranibizumab
It looks like the price for ranibizumab was from 2011 (citation 4 says September 2011), prior to the updated negotiated price in the patient access scheme:
http://www.nice.org.uk/newsroom/pressreleases/DraftGuidanceYesRanibizumabCommonEyeCondition.jsp
Although the terms of that agreement are “commercial in confidence”, it would be nice to see a more thorough sensitivity analysis on ranibizumab price.
RESPONSE: Within our base case analysis, we assumed that ranibizumab cost £742.17 per dose (excluding VAT), which is the current list price stated on the website of the British National Formulary (http://www.medicinescomplete.com/mc/bnf) and has not changed since the 2011 edition of the BNF that we used as a source of all drug costs within our analysis. We recognise that a discount was negotiated as part of the patient access scheme that was revised in 2012. However, the size of this discount is commercial in confidence and so we were unable to use the discounted price in our base case analysis or in sensitivity analyses. We therefore used the list price in the base case analysis and conducted extensive sensitivity analyses, which demonstrated that the conclusions of our analysis would hold unless hospitals received a 91% discount off the list price of ranibizumab. Figure 3 presents the results of 4 sensitivity analyses varying the price of ranibizumab, including a 25% discount and a 50% discount off the list price, as well as the patient access scheme agreed in 2008 (in which the NHS incurred no cost after each patient’s 15th injection) and a “best case” analysis, which discounts the list price of ranibizumab by 50% as well as changing other assumptions in favour of ranibizumab. We also conducted threshold analysis (described in the second paragraph in the sensitivity analysis section) in which we considered all possible prices of ranibizumab in order to identify the price at which continuous ranibizumab would be cost-effective and which shows that a 91% discount would be required to make ranibizumab cost-effective. We therefore don’t feel that any further sensitivity analyses on ranibizumab price are necessary. Since the probability of ranibizumab being cost-effective was <1% even when its list price was discounted by 50%, we don’t feel that using the list price has limited generalisability or that any additional caveats are required. However, we have drawn attention to the sensitivity analyses on the list price in the first paragraph of the sensitivity analyses section and acknowledged this limitation in the penultimate paragraph of the discussion “Although hospitals receive a commercial-in-confidence discount off the list price of ranibizumab and the price of bevacizumab varies between hospitals, the conclusions were robust to substantial changes in drug price”.

Discussion:

The authors may wish to be a little more circumspect in some of the conclusions.
These conclusions are based on the IVAN trial experience. This analysis does not use data from CATT or current UK pricing of ranibizumab.
RESPONSE: We fully acknowledge that IVAN is one of a number of trials comparing ranibizumab and bevacizumab. We hope to do a broader economic evaluation in the future that estimates cost-effectiveness based on all relevant evidence, although this is beyond the scope of this current paper. In response to this comment, we have added two sentences in the penultimate paragraph of the discussion to say that “The analysis also uses data only from IVAN, rather than synthesising all available evidence” and that “Although hospitals receive a commercial-in-confidence discount off the list price of ranibizumab and the price of bevacizumab varies between hospitals, the conclusions were robust to substantial changes in drug price.” However, for the reasons discussed in relation to the previous comment, we don’t feel that using the list price of ranibizumab warrants any other change in the wording of our conclusions.

Page 15, Lines 23-26:

“This study demonstrates that in a UK setting, we can be >99% confident that ranibizumab represents very poor value for money compared with bevacizumab at the £20,000 ($31,000) per QALY ceiling ratio used within NHS decision-making.”
Since we do not know that the current UK pricing is representative of the prices used in the IVAN study, it may be more accurate to say, “This study demonstrates that in the setting of the IVAN trial in the UK, we can be >99% confident that ranibizumab represented very poor value for money compared with bevacizumab at the £20,000 ($31,000) per QALY ceiling ratio used within NHS decision-making.”
RESPONSE: We have revised this sentence to read “This study demonstrates that in the setting of the UK IVAN trial, we can be >99% confident that ranibizumab represents very poor value for money compared with bevacizumab at the £20,000 ($31,000) per QALY ceiling ratio used within NHS decision-making.”

Pages 15 , line 54- page 16, line 4
“CATT and IVAN provide robust data to guide regulators in this decision, demonstrating that ranibizumab and bevacizumab have comparable effects on vision and similar safety profiles,6 7 but that ranibizumab costs £3.5 million per QALY compared with bevacizumab.”
I agree with the first part of that sentence. The second part would suggest that the CATT results also suggest that ranibizumab costs £3.5 million per QALY compared with bevacizumab (which this study does not show).
I might say something like, “CATT and IVAN provide robust data to guide regulators in this decision, demonstrating that ranibizumab and bevacizumab have comparable effects on vision and similar safety profiles,6 7 but this analysis of IVAN shows that to the extent ranibizumab has better health outcomes, they cost £3.5 million per QALY compared with bevacizumab.”
RESPONSE: In response to this comment, we have rephrased this sentence to say that: “CATT and IVAN provide robust data to guide regulators in this decision, demonstrating that ranibizumab and bevacizumab have comparable effects on vision and similar safety profiles,6 7 but that (based on the current analysis of IVAN) ranibizumab costs £3.5 million per QALY compared with bevacizumab.”

Page 17, lines 51-55:
“For example, the incidence of SAEs was substantially lower in IVAN than CATT,6 7 although sensitivity analyses suggested that this did not change the conclusions.”
It’s my understanding that the sensitivity analysis performed here examined including the SAE’s observed in IVAN. Did the authors also examine SAE rates as high as those observed in CATT?
RESPONSE: We conducted a sensitivity analysis in which the QALY impact and cost of each SAE observed in IVAN was doubled (labelled as “doubling SAE impact” in Figure 3), which is equivalent to a doubling of the incidence of SAEs. We have also added additional information in the legend of Figure 3 to clarify what was done in this sensitivity analysis. Since 28% of IVAN participants had SAEs,1 compared with 36% of those in CATT2, this sensitivity analysis amply allows for the observation that the total incidence of SAEs is much higher in CATT than in IVAN. In response to this comment, we have rephrased this sentence to say: “For example, the incidence of SAEs was substantially lower in IVAN than CATT,1 2 although sensitivity analyses doubling the impact of SAEs on costs and QALYs suggested that this did not change the conclusions”.

Discussion:
It would be good to comment on the relatively short time horizon (presumably, patients with AMD will be receiving these injections for the rest of their lives). I would presume that since the health outcomes seemed very similar between ranibizumab and bevacizumab, and there did not appear to be a trend in year 2, that we would expect these results to hold over a longer time period. The differences between continuous and discontinuous may be more difficult to discern over this 2-year time horizon of analysis.

RESPONSE: In response to this comment, we have added two sentences in the discussion to say: “The study focused on the period of follow-up in the trial and excluded costs and benefits beyond Year 2. However, since incremental costs and QALYs remained reasonably stable over time this is unlikely to have affected the conclusions.”

Reviewer Name Thomas Butt
Institution and Country UCL Institute of Ophthalmology
University College London

The manuscript describes the cost effectiveness of bevacizumab compared with ranibizumab for age-related macular degeneration using cost minimisation analysis and the cost effectiveness of continuous compared with discontinuous treatment using cost-utility analysis. The study is a within trial economic evaluation using the IVAN randomised trial.

Minor comments:
p4 line 17: I expect there have been evaluations of anti-VEGF vs. vPDT for nAMD, so consider clarifying to "of alternative anti-VEGF treatment regimens"
RESPONSE: In response to this comment and a comment from Reviewer 1, we have revised this sentence to read “Our study is the first trial-based economic evaluation to evaluate the cost-effectiveness of alternative anti-VEGF treatments for nAMD”.

p9 line 6: If possible, please comment on how the not-for-profit NHS provider price per syringe compares with the list price for bevacizumab, allowing for dosing.
RESPONSE: The list price of Avastin is currently £242.66 for a 100 mg vial and £924.40 for a 400 mg vial, which equates to a substantially higher cost per unit and substantially lower cost per mg than the provider price used in this analysis (£49 for 1.25 mg). If the BMJ Open house style permits footnotes, we would be happy to add a footnote after “£49” saying “This equates to a cost of £39.20 per mg, compared with a list price of £242.66 (£2.43/mg) for a 100 mg vial and £924.40 (£2.31/mg) for a 400 mg vial.4” However, we don’t feel that such a footnote would add much to the paper, since the 2011 list price of the 100 mg vial is already stated in Figure 3 and it would not be possible to split Avastin vials without wastage or be likely that any hospitals would use a whole 100 mg vial per patient.

p10, line 45: Please confirm whether QALYs were also discounted in year 2.
RESPONSE: We have revised this sentence to state that both costs and QALYs were discounted at 3.5% per annum. We thank the reviewer for alerting us to this omission.

p11, line 50: Were 13 discontinuous injections distributed evenly across the two years? If there was a trend upwards or downwards, would this have implications for cost-effectiveness of continuous vs. discontinuous regimens over a longer time horizon.
RESPONSE: With the exception of Quarter 1 (when all patients received three injections), the differences in the number of injections appears to be relatively constant over time. In response to this comment, we have added two sentences in the discussion to say: “The study focused on the period of follow-up in the trial and excluded costs and benefits beyond Year 2. However, since incremental costs and QALYs remained reasonably stable over time this is unlikely to have affected the conclusions.”

p15 line 2: Please confirm whether the pre-specified non-inferiority margin of 0.05 QALYs (p12) was also met using HUI-3-derived utilities?
RESPONSE: The pre-specified non-inferiority margin was met for the base case analysis (EQ-5D utilities), but not HUI3 utilities. Our statistical analysis plan specified that in the case where interactions were significant or change the conclusions, CMA would be conducted unless mean EQ-

5D QALYs for continuous ranibizumab were ≥0.05 higher than those for continuous bevacizumab. In the sensitivity analysis that used HUI3 utilities, the difference in QALYs was 0.088 (1.394 versus 1.306), which suggests that this sensitivity analysis should be interpreted based on the joint distribution of costs and QALYs, rather than by a comparison of costs, which is in fact what we have done in Figure 3 for all sensitivity analyses. Since the analysis of HUI3 utilities is only a sensitivity analysis and we are keen to keep the paper clear and succinct, we have not discussed the difference in QALYs for this analysis in any great detail, although we will ensure that this is discussed in the HTA monograph, which presents the results and methods in more detail. However, we have added a specific mention in the last paragraph before the "Measurement and valuation of resource use" heading to say that the non-inferiority margin is based on EQ-5D utilities.

p15 line 35: Does 17,295 eyes requiring anti-VEGF therapy already include some eyes treated with bevacizumab? If so, the estimated saving from switching may be lower
RESPONSE: Following NICE's recommendation of ranibizumab, bevacizumab is rarely used to treat patients with nAMD in the UK. We therefore feel that it is reasonable to estimate the savings from switching treatment based on the assumption of all patients being switched from ranibizumab to bevacizumab.

Time horizon: the use of a two-year time horizon for an economic evaluation of a chronic condition warrants some discussion.
RESPONSE: In response to this comment, we have added two sentences in the discussion to say: "The study focused on the period of follow-up in the trial and excluded costs and benefits beyond Year 2. However, since incremental costs and QALYs remained reasonably stable over time this is unlikely to have affected the conclusions." We have also added in a justification of the time horizon in the first paragraph of the methods: "The economic evaluation took a two-year time horizon to estimate within-trial cost-effectiveness since incremental costs and QALYs appeared to be relatively stable over time."

Text:
p3 line 9: abbreviate NHS
RESPONSE: In response to this comment, we have defined the abbreviation NHS in the objectives of the abstract, since the instructions to authors state that acronyms should be used sparingly and fully defined when first used. We will leave it up to the editors whether the acronym NHS is sufficiently well-known for it to be used in the abstract without definition.

p3 line 51: consider revising 'little/no' to one or the other
RESPONSE: In response to this comment, we have revised this to read "little or no QALY gain". We feel that this wording is most appropriate in this context since continuous ranibizumab generates 0.004 more QALYs than continuous bevacizumab, whereas discontinuous ranibizumab generates 0.002 fewer QALYs than discontinuous bevacizumab.

p5 line 14: £742/dose in the UK
RESPONSE: The words "in the UK" have been added as suggested.

p9 line 45: abbreviate ETDRS
RESPONSE: We have added the abbreviation ETDRS after the full name of this vision chart as suggested.

p12 line 8: expand FFA
RESPONSE: Fundus fluorescein angiography (FFA) is defined at its first use (page 8) and is abbreviated thereafter, since it is used four times in the text in addition to four times in Figure 1. We have therefore not expanded this abbreviation but would be happy to do so if the editors feel this is

appropriate.

1. Chakravarthy U, Harding SP, Rogers CA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet 2013;382(9900):1258-67.
2. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration: Two-Year Results. Ophthalmology 2012;119(7):1388-98.
4. British Medical Association. British National Formulary 62 (http://bnf.org/bnf/index.htm). London: Pharmaceutical Press, September 2011.